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VOL.
1
1962/

OL.
1
62/63

JOURNAL OF PSYCHIATRIC RESEARCH

VOLUME 1 NUMBER 1 OCTOBER 1961

CONTENTS

Page

W. DINGMAN and M. B. SPORN: The incorporation of 8-azaguanine into rat brain RNA and its effect on maze learning by the rat: an inquiry into the biochemical basis of memory 1

V. G. LATIES: Modification of affect, social behaviour and performance by sleep deprivation 12

DAVID ROSENTHAL: Sex distribution and the severity of illness among samples of schizophrenic twins 26

PHILIPPE V. CARDON, LOUIS SOKOLOFF, THOMAS S. VATES and SEYMOUR S. KETY: The physiological and psychological effects of intravenously administered epinephrine and its metabolism in normal and schizophrenic men — I. Effects on heart rate, blood pressure, blood glucose concentration and the electroencephalogram 37

WILLIAM POLLIN and SAMSON GOLDIN: The physiological and psychological effects of intravenously administered epinephrine and its metabolism in normal and schizophrenic men — II. Psychiatric observations 50

ELWOOD H. LABROSSE, JAY D. MANN and SEYMOUR S. KETY: The physiological and psychological effects of intravenously administered epinephrine, and its metabolism, in normal and schizophrenic men — III. Metabolism of 7-H^3-epinephrine as determined in studies on blood and urine 68

RUDOLF HÖHN, GERTRUDE M. GROSS, MARTIN GROSS and LOUIS LASAGNA: A double-blind comparison of placebo and imipramine in the treatment of depressed patients in a state hospital 76

K. WARNER SCHAIE, LOIS R. CHATHAM and JAMES M. A. WEISS: The multiprofessional intake assessment of older psychiatric patients 92

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JOURNAL OF PSYCHIATRIC RESEARCH

VOLUME 1 NUMBER 2 SEPTEMBER 1962

VOL.
1
1962/

CONTENTS

	Page
D. D. BROWN, O. L. SILVA and P. MCDONALD: A comparison of the urinary metabolites of L-histidine-C^{14} in schizophrenic and normal subjects	101
P. S. MUELLER: Plasma free fatty acid concentrations (FFA) in chronic schizophrenia before and after insulin stimulation	106
D. ROSENTHAL: Problems of sampling and diagnosis in the major twin studies of schizophrenia	116
M. ROSENBERG: The association between self-esteem and anxiety	135
R. GREEN and J. MONEY: Binocular rivalry of gender-significant picture in a stereoscope	153
J. L. GIBBONS and P. MCHUGH: Plasma cortisol in depressive illness	162

PRINTED IN GREAT BRITAIN AT THE BAY TREE PRESS, STEVENAGE, HERTS.

OL.
1
62/63

JOURNAL OF PSYCHIATRIC RESEARCH

VOLUME 1 NUMBER 3 DECEMBER 1962

CONTENTS

	Page
R. K. McDONALD and V. K. WEISE: The excretion of 3-Methoxy-4-Hydroxymandelic acid in normal and in chronic schizophrenic male subjects	173
N. TRANEL: Effects of perceptual isolation on introverts and extraverts	185
T. LIDZ, C. WILD, S. SCHAFER, B. ROSMAN and S. FLECK: Thought disorders in the parents of schizophrenic patients: A study utilizing the object sorting test	193
D. N. O'CONNELL and M. T. ORNE: Bioelectric correlates of hypnosis: An experimental reevaluation	201
A. YUWILER and M. H. GOOD: Chromatographic study of "Reigelhaupt" chromogens in urine	215
H. BUSCHKE: Auditory and visual interaction in immediate memory	229
J. E. OVERALL: Dimensions of manifest depression	239
V. R. CARLSON and I. FEINBERG: Response-times of schizophrenics in a perceived velocity task	247

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JOURNAL OF PSYCHIATRIC RESEARCH

VOLUME 1 NUMBER 4 DECEMBER 1963

CONTENTS

	Page
MAURICE LORR, DOUGLAS M. MCNAIR and GEORGE J. WEINSTEIN: Early effects of chlordiazepoxide (librium) used with psychotherapy	257
C. M. B. PARE and ELWOOD H. LABROSSE: A further study on alleviation of the psychological effects of LSD in man by pretreatment with 5-hydroxy-tryptophan	271
P. H. VENABLES: The relationship between level of skin potential and fusion of paired light flashes in schizophrenic and normal subjects	279
GERALD L. KLERMAN, JOSEPH J. SCHILDKRAUT, L. LEE HASENBUSH, MILTON GREENBLATT and DALE G. FRIEND: Clinical experience with dihydroxyphenylalanine (DOPA) in depression	289
WILLIAM A. MASON and R. R. SPONHOLZ: Behavior of rhesus monkeys raised in isolation	299

VOL.
1
1962/

PRINTED IN GREAT BRITAIN AT THE BAY TREE PRESS, STEVENAGE, HERTS.

THE INCORPORATION OF 8-AZAGUANINE INTO RAT BRAIN RNA AND ITS EFFECT ON MAZE-LEARNING BY THE RAT: AN INQUIRY INTO THE BIOCHEMICAL BASIS OF MEMORY*

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OL.
1
62/63

THIS investigation represents an attempt to develop a testable hypothesis for the biochemical basis of memory. A prerequisite for such an attempt is an adequate definition of the concept of memory. In his book, *Design for a Brain*, ASHBY [1] notes that "'Learning" and "memory" have been given almost as many definitions as there are authors to write of them . . . but the theme is that *a past experience has caused some change* [italics ours] in the organism's behavior . . .". Ashby also emphasizes the tenacity with which memory traces may persist; the persistence of such traces gives adaptive potential to the organism. Memory must therefore involve two processes: (1) the process of transition of a system to a new state and (2) the persistence of that new state. At this point, we shall distinguish between the terms "memory", "memory trace", "recall" and "learning", as they will be used in this paper. While memory is the *process* of transition of a system to a new state and the persistence of the new state, a memory trace is the particular new state that has been formed. Recall is the process of using a memory trace. Learning then is defined as any process in which one can demonstrate the processes of memory and recall. We should also like to make a distinction between our use of the terms "memory" and "memory in the psychological sense". "Memory" will be used to include all manifestations (not necessarily limited to the nervous system) of the process of memory as it has just been defined, while "memory in the psychological sense" will refer only to those aspects of memory which can be observed by psychological techniques.

Having thus defined memory, we shall cite three biological systems in which the process of memory (considered in its broadest sense) occurs and which are not often included in discussions of this phenomenon. Consideration of these examples might provide insight into some of the possible biochemical mechanisms involved in the processes of memory in the nervous system. The first example is the formation of a new gene by the process of mutation. In agreement with our definition of memory, genes may undergo transition to a

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new state by the process of mutation, and the new state formed has the potentiality to persist. One might therefore say that the new gene formed is a memory trace of the event (e.g., exposure to ionizing radiation) that led to mutation. Present evidence which indicates that the gene is composed of deoxyribonucleic acid (DNA) or DNA plus a basic protein, has been reviewed by BRACHET[2] and SINSHEIMER[3]. Pertinent to our discussion is the fact that DNA is metabolically stable and yet subject to transformation.

The second example is antibody formation. An antibody is a memory trace of an organism's experience with a foreign substance. The elaboration of a new antibody is the expression of a transition (of certain protein molecules) to a new state, and the persistence of this new state is well known. Not so well understood is the biochemical basis of antibody production. Antibodies are known to be highly specific proteins[4], but their mode of synthesis is still in question. While there is abundant unquestioned evidence for some intimate relationship between ribonucleic acid (RNA) and protein synthesis, the nature of this relationship is still a matter of controversy. One widely held opinion, which BRACHET[2] and LOFTFIELD[5] have reviewed, is that specific RNA directs the synthesis of specific proteins.

The third example is the formation of adaptive enzymes. This phenomenon, extensively studied in yeast and bacteria, is again an example of the occurrence of some transformation (i.e., the formation of new enzyme molecules) in the organism. This transformation occurs as the result of an organism's experience with a substrate which it previously was unable to metabolize, and the new enzyme molecules formed have the ability to persist. Enzymes, like antibodies, are highly specific proteins whose mode of synthesis is not completely understood. However, several investigators have shown that RNA may play an important role in the synthesis of adaptive enzymes: GALE and FOLKES[6] found that *Staph. aureus* cells, which had had most of their RNA extracted, could be induced to form β-galactosidase only in the presence of all of the following components: galactose, a complete mixture of essential amino acids, and a mixture of purines and pyrimidines. They also noted that just preceding and during the synthesis of β-galactosidase by this system there was a net uptake of C^{14}-uracil into newly synthesized RNA. KRAMER and STRAUB[7] showed that the synthesis of penicillinase could be induced in *B. cereus*, in the absence of penicillin, if the growing bacteria were incubated with RNA extracted from another strain in which penicillinase was normally present. The inductive substance lost all its potency when treated with ribonuclease. CHANTRENNE[8] found that the induction of an enzyme was accompanied by increased incorporation of labeled adenine and uracil into yeast RNA, and that different RNA fractions did not show the same relative increase under these conditions.

Some interesting effects on adaptive enzyme formation have been obtained using analogues of the purines and pyrimidines found in nucleic acids: COURTOIS and CHANTRENNE[9] showed that thiouracil inhibited catalase formation in baker's yeast; SPIEGELMAN *et al.*[10] found that 5–hydroxyuridine inhibited β-galactosidase synthesis in *E. coli;* and CREASER[11] showed that 8–azaguanine and 2,6-diaminopurine inhibited the synthesis of β-galactosidase in *Staph. aureus.* Continuing with these investigations, CREASER[12] found that 8–azaguanine was incorporated into the RNA of *Staph. aureus*, and that in the concentrations which markedly impaired the formation of β-galactosidase and catalase, it did not impair the uptake of C^{14}-uracil into RNA. The incorporation of 8-azaguanine into RNA has also been observed in other systems. MATTHEWS[13] found that tobacco mosaic virus incorporated this

VOL.
1
1962/

purine analog and subsequently showed a decreased infectivity. In summary, there is much evidence for the conclusion of PARDEE[14] and SPIEGELMAN *et al.* [10] that proper RNA synthesis is essential for the formation of adaptive enzymes.

Thus in the three examples of memory cited above nucleic acids are thought to play an important, if not a decisive, role. Mutation, antibody synthesis, and adaptive enzyme synthesis are all examples of a biological system's ability to undergo transition to a new state and to have this new state persist. The fact that these transitions are intimately linked with the metabolism of nucleic acids has been amply shown. We are, therefore, proposing the hypothesis that the process of memory in the psychological sense is intimately connected with ribonucleic acid. In our hypothesis memory traces in the nervous system are formed by changing the primary (nucleotide sequence), secondary (helix content), or tertiary (pattern of folding) structure of an RNA molecule. All that is required is that the new state formed has different functional properties and that it persists. During the course of the investigations reported in this paper a similar hypothesis (but involving changes only in primary structure of RNA) on the role of RNA in formation of memory traces in the nervous system was put forth by HYDÉN[15]. In agreement with the needs of such an hypothesis, recent experimental work has shown that the brain has a very dynamic nucleic acid and protein metabolism [16–22]. Our hypothesis does not specify the method by which inputs cause formation of altered RNA; but one may visualize, as a possibility, the input's causing some transient change in intraneuronal conditions which results in an altered RNA molecule. It is pertinent to note that the secondary and tertiary structure of RNA in solution is extremely sensitive to changes in ionic environment [23, 24]. It should be emphasized that our hypothesis in no way excludes the importance of the synapse, or of neuronal pathways, as vital parameters of brain function. Rather the hypothesis is an attempt to deal with certain critical metabolic processes whose function in turn may determine the behavior of synapses or neuronal pathways.

The remainder of this paper deals with an attempt to gain evidence for the above hypothesis. An experiment which makes use of the analogy between the formation of adaptive enzymes and the formation of memory traces in the nervous system will be described. It was shown that intracisternally injected 8-azaguanine–2–C^{14} was incorporated into rat brain RNA and that intracisternally injected 8-azaguanine, while it did not impair a rat's ability to recall and perform a previously well-learned maze, did impair a rat's acquisition of perfection in a new maze, the result suggesting a possible interference by 8-azaguanine of the rat's ability to learn a new maze. 8-Azaguanine was used as the inhibitor of RNA because of the abundant evidence that this antimetabolite is incorporated into RNA [13, 25–28] and because it has been shown to be a potent inhibitor of adaptive enzyme formation[12].

METHODS AND RESULTS

1. *Incorporation of 8-azaguanine-2-C^{14} into brain RNA*

Purity of 8-azaguanine-2-C^{14}. 8-Azaguanine-2-C^{14} (Isotope Specialities Co., Burbank, Calif.) was recrystallized from dilute NaOH prior to use. Examination of this material after paper chromatography in isopropanol-HCl[29] and *n*-butanol-diethylene glycol-HCl[30]

showed that it gave a single spot, which fluoresced brightly in ultraviolet light of 2537 Å, and a single peak of radioactivity, with an R_f corresponding to a known sample of 8-azaguanine.

Determination of radioactivity. All counting was done in the Geiger region with a gas flow counter fitted with an end-window. All samples were at infinite thinness, were plated in duplicate, and were counted for no less than 1000 counts. All counts reported are those actually measured on the counter and have been corrected for background radiation.

Injection of rats and preparation of brain homogenates. Male albino rats, 3–4 months old, of the Sprague–Dawley strain* were used in all experiments. All injections were performed under light ether anesthesia, using a microsyringe calibrated to 0·0001 ml† Rats were injected intracisternally with 0·01 ml of a solution containing 132 μg of 8-azaguanine-2-C^{14} (giving 1,120,000 counts/min), dissolved in 0·150 M HCO_3^- solution (0·145 M in Na^+, 0·005 M in K^+). All rats were alert and walking within no more than 8 min after their injections. Groups of six animals were sacrificed 15, 30 and 60 min after injection, their brains rapidly removed, cleaned of meninges, blotted with filter paper to remove any surface blood and homogenized in a Potter–Elvehjem homogenizer in 15 ml of water at 0°–1°C. The homogenates were immediately poured into an equal volume of liquefied 90% phenol and stirred for 1 hr at room temperature.

Preparation and analysis of RNA from brain. RNA was isolated from brain homogenates by extraction with an aqueous solution of phenol followed by precipitation with ethanol [31]. The yield of RNA, after three reprecipitations, is about 1 mg/g wet weight brain. RNA was determined by the orcinol procedure [32]. The powdery, white brain RNA isolated in the above procedure was 15·2% N and 8·8% P, with an atomic N/P ratio of 3·9. This material gave a chromatogram identical to commercial yeast RNA upon hydrolysis in 1N HCl at

TABLE 1. SPECIFIC ACTIVITY OF BRAIN RNA AFTER INJECTION OF 8-AZAGUANINE-2-C^{14}

Time between injection and sacrifice (min)	Specific activity of RNA (counts/min/mg RNA)
15	128
30	215
60	58

100° for 1 hr, followed by chromatography in *t*-butanol-HCl [33]. Radioactivity in the isolated RNA is shown in Table 1; maximum specific activity was found at 30 min after injection of 8-azaguanine-2-C^{14}, with a rapid decline of activity in the period 30–60 min. For a rat with a brain weight of 1·7–1·8 g (which would contain approximately 2·5 mg of RNA), the percentage of injected 8-azaguanine-2-C^{14} recovered in total brain RNA 30 min after injection was approximately 0·05%.

* Holtzman Co., Madison, Wis.
† Nuclear Science Associates, Newark, N.J.

VOL. 1 1962/

Further experiments were conducted to determine whether the radioactivity in the RNA represented true incorporation of 8-azaguanine into nucleic acid. The following alternative possibilities exist: (1) 8-azaguanine was not actually incorporated into brain RNA, but was merely physically adsorbed; and (2) 8-azaguanine was metabolized to some other azapurine, such as 8-azaadenine or 8-azaxanthine, which was subsequently incorporated into or adsorbed onto brain RNA. These possibilities were investigated by paper chromatographic analysis of acid and alkaline hydrolysates of brain RNA isolated after injection of 8-azaguanine-2-C^{14}.

Acid hydrolysis of RNA was done in 1 N HCl at 100° for 1 hr, following addition of carrier 8-azaguanine, 8-azaadenine, and 8-azaxanthine. Alkaline hydrolysis was done in 0·3 N NaOH at 37° for 18 hr[34], following addition of carrier 8-azaguanine. The acid hydrolysis degrades RNA to purine bases and pyrimidine nucleotides, while the alkaline hydrolysis liberates purine and pyrimidine nucleotides. The hydrolysates were chromatographed on Whatman No. 3 paper in *n*-butanol-dioxane-1 N HCl (4:1:1). In this system the following R_f's are observed: guanine 0·09, adenine 0·18, 8-azaguanine 0·36, 8-azaadenine 0·28, 8-azaxanthine 0·62, guanylic acid 0·13, adenylic acid 0·14, cytidylic acid 0·16 and uridylic acid 0·52. 8-Azaguanine is thus clearly separated from any of the compounds that might reasonably be expected to arise from either acid or alkaline hydrolysis of RNA. The eluates from the paper chromatograms of the acid hydrolysate showed that over ninety-five per cent of the radioactivity in the hydrolysate was accounted for by 8-azaguanine. This rules out the possibility that a significant amount of the radioactivity in the RNA was from substances other than 8-azaguanine. The eluates from the paper chromatograms of the alkaline hydrolysate showed that only seventeen per cent of the total counts on the paper traveled with 8-azaguanine, thus indicating that the majority of counts were not the result of physical adsorption of 8-azaguanine-2-C^{14} onto brain RNA. One may therefore conclude that 8-azaguanine-2-C^{14} is incorporated into rat brain RNA.

2. *Effect of 8-azaguanine on acquisition of perfection in a maze*

Several experimentally testable processes are involved in a rat's acquisition of perfection in a maze. Among these are: (1) proper functioning of the modalities necessary for performance of a maze test (such as vision, neuromuscular coordination and proprioception), (2) recall and (3) learning (which includes both memory and recall). The following two experiments were designed to study the effect of 8-azaguanine on acquisition of perfection in a maze: Experiment A was designed to measure the effect of 8-azaguanine on performance and recall, while Experiment B was designed to measure the effect of 8-azaguanine on learning.

Design and operation of water maze. The water maze, basically of the design of ROSVOLD and MIRSKY[35], consisted of a tank 30 in. square by 12 in. deep, with a starting area at one end and an escape ladder diagonally opposite. The tank was lined with sheet copper and there were copper baffles interposed between the starting area and the escape ladder. The pattern of arrangement of these baffles for Mazes 1, 2 and 3 is shown in Fig. 1. The tank was filled to within 2 in. of the top with water maintained at 15° ± 1°C; in water of this temperature a rat was motivated to swim from the starting area to the escape ladder.

A 30-inch-square wire screen, marked with thin tape into 7½-in. squares (thus producing

a total of sixteen squares for the entire screen) covered the tank and thereby divided the maze (from a vertical perspective) into sixteen imaginary squares. An observer made a tracing (on a standard mimeographed diagram) of each individual run through the maze, and the total number of squares that a rat traversed in going from start to finish could thus be counted. An incorrect turn by a rat at a choice point was classified as an error. By measuring the total time it took to swim from start to finish and by counting the number of squares entered, one could compute the number of squares traversed per second, which is a measure of the rate of swimming, i.e. the ability to perform swimming movements.

Experiment A. Effect of 8-azaguanine on recall and performance. This experiment was conducted as follows: sixteen young adult rats, which had never been in a maze previously, were trained (at a rate of fifteen trials per day) to swim Maze 3 until they had swum it to a criterion of fifteen consecutive perfect trials. On the basis of the number of trials to reach this criterion, the sixteen rats were equated and then divided into two groups of eight, called control and 8-azaguanine. The control group was injected intracisternally (under light ether anesthesia) with 0·01 cm^3 of a solution that was 0·150 M in HCO_3^-, 0·145 M in Na^+ and 0·005 M in K^+; the 8-azaguanine group was injected intracisternally (under light ether anesthesia) with 0·01 cm^3 of a solution that contained 136μg of 8-azaguanine dissolved in a bicarbonate solution identical to that which the control group received. All animals in both groups received their intracisternal injections 30 min after reaching criterion. All animals were given a single retest trial in Maze 3, 15 min after their intracisternal injections and each rat was scored both for squares traveled per second and total errors. A single retest trial was used in order to eliminate the possibility of further learning of the maze and thus measure recall alone.

The results of these experiments are shown in Table 2, which includes t values for possible

TABLE 2. EFFECT OF 8-AZAGUANINE ON RECALL AND PERFORMANCE OF A PREVIOUSLY LEARNED MAZE (EXPERIMENT A)

SQUARES TRAVERSED PER SECOND ON RETEST OF MAZE 3

Group	Rats No.	Mean squares traversed per second ± standard error of mean	t	p
Control	8	1·1 ± 0·1	0·9	>0·30
8-azaguanine	8	1·0 ± 0·0		

ERRORS MADE ON RETEST OF MAZE 3

Group	Rats No.	Mean errors ± standard error of mean	t	p
Control	8	0·3 ± 0·2	1·2	>0·20
8-azaguanine	8	0·6 ± 0·3		

differences between the two groups. It can be seen from the t values that there is no statistically significant* difference between the two groups of animals in their ability to recall and perform Maze 3 and therefore, that there is little evidence that 8-azaguanine exerts any significant effect on the ability of a rat to recall and perform Maze 3 once it has been learned.

Experiment B. Effect of 8-azaguanine on learning. The experiments on the effect of 8-azaguanine on the learning of Maze 3 were carried out as follows: thirty-two young adult rats, which had never been in a maze previously, were pretrained at a rate of fifteen trials per day first on Maze 1 and then on Maze 2 (Fig. 1) until they had scored five consecutive errorless trials in each maze. Based on their learning scores in Maze 1 and Maze 2, the rats were equated and then divided into two groups, called control and 8-azaguanine. The control and 8-azaguanine groups were injected in the same manner and with the same doses of material as their counterparts in Experiment A. Fifteen minutes after intracisternal injection, each rat was placed in Maze 3 and given fifteen consecutive trials in the maze at intervals of three minutes, with squares traveled per second and total errors again being recorded†. The results of these experiments are shown in Table 3 and in Fig. 2. Both

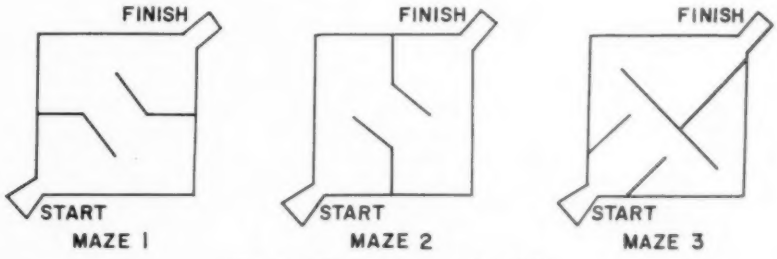

FIG. 1. Plan of Mazes 1, 2 and 3.

groups of rats had essentially identical values for squares traversed per second, indicating once again that the intracisternal injection of 8-azaguanine did not impair ability to perform in the maze.

The 8-azaguanine group of animals made an average of thirty errors in fifteen trials, as contrasted with an average of fifteen errors for the controls. In spite of the wide spread of the data in each of the two groups, the calculated value for t (on the basis of fifteen trials) indicates that the probability of obtaining such samples from a single population is less than five per cent.

---

* Values of p greater than 0·05 will not be considered statistically significant in this paper.

† For the learning study it was arbitrarily decided to remove any rat from the maze one minute after the start of any trial if that rat had not yet reached the finish. Rats were thus prevented from becoming fatigued before completing fifteen trials. Three rats (two control and one 8-azaguanine) were discarded from the study because their performance necessitated removal from the maze on six or more occasions (no rat included in the reported data was removed more than twice). These rats had scores which differed by four standard deviations from the mean of their respective groups in terms of squares traversed per second. This unusual behavior may have been caused by brain damage sustained during intracisternal injection. The removal of these rats in no way changed the equivalence of the two groups with respect to their learning scores on Mazes 1 and 2.

TABLE 3. EFFECT OF 8-AZAGUANINE ON PERFORMANCE AND LEARNING OF A NEW MAZE (EXPERIMENT B)

SQUARES TRAVERSED PER SECOND IN 15 TRIALS ON MAZE 3

Group	Rats No.	Mean squares traversed per second ± standard error of mean	t	p
Control	14	1·6 ± 0·1	1·1	>0·20
8-azaguanine	15	1·5 ± 0·1		

TOTAL ERRORS MADE IN 15 TRIALS ON MAZE 3

Group	Rats No.	Mean total errors ± standard error of mean	t	p
Control	14	15 ± 4·6	2·3	<0·05
8-azaguanine	15	30 ± 4·9		

ERRORS MADE ON FIRST TRIAL OF MAZE 3

Group	Rats No.	Mean errors ± standard error of mean	t	p
Control	14	2·7 ± 0·9	2·8	<0·01
8-azaguanine	15	7·0 ± 1·4		

As can be seen from the learning curves in Fig. 2, the greatest differences in mean errors per trial between the two groups of animals were found during approximately the first third of the learning experiment (i.e., during the time period 15–30 min after intracisternal injection). In this connection it is of interest that in the tracer experiments described in Table 1, the maximum labeling of RNA with 8-azaguanine-2-C^{14} occurred 30 min after intracisternal injection of the radioisotope. The particularly large difference between the two groups of animals on the first trial (as shown in Table 3) is a result of the large number of repetitive errors made by the rats given 8-azaguanine, and the confidence level that the groups represent a single population (on the basis of the first trial only) is less than one per cent. The less pronounced differences between the two learning curves during the latter part of the experiment illustrated in Fig. 2 may reflect the rapid decline in the amount of 8-azaguanine in RNA during the time period 30–60 min after intracisternal injection.

It should be noted that the inhibitory effects of 8-azaguanine on acquisition of perfection in a new maze observed in Experiment B are by no means absolute, and that the group of animals injected with 8-azaguanine was definitely capable of partial learning of Maze 3. However, the control group of animals were superior in their error scores to the

VOL. 1 1962/

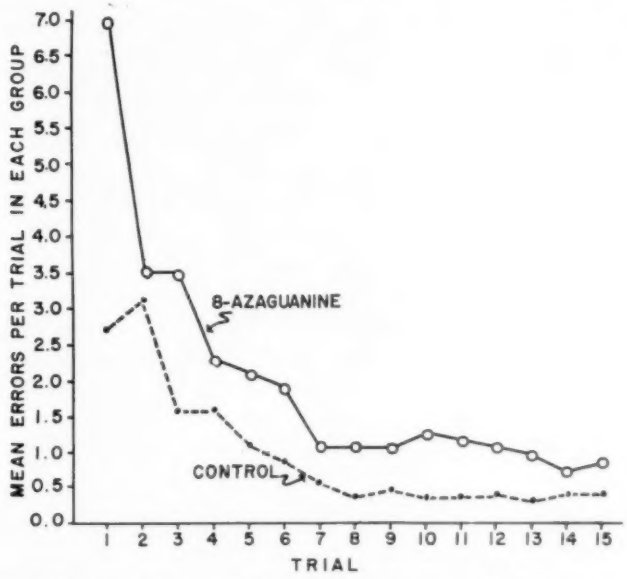

FIG. 2. Effect of 8-azaguanine on the learning of a new maze (Experiment B).

8-azaguanine group at all stages of Experiment B. Inasmuch as both groups had essentially identical values for squares traversed per second, it would appear that gross differences in activity levels between the two groups could not account for the observed differences in learning, although more subtle differences between the groups with regard to motivational factors and motor activity conceivably may have contributed to differences in learning.

DISCUSSION

Although it was found that 8-azaguanine: (1) is incorporated into brain RNA and (2) has an inhibitory effect on the acquisition of perfection in a new maze (in the manner that this process has been previously discussed), these results do not prove that RNA metabolism is intimately linked with the formation of memory traces in brain. There is the possibility that 8-azaguanine interferes with metabolic processes which are: (1) necessary for memory, but not directly related to RNA metabolism; (2) necessary for proper motivation to learn; or (3) necessary for adequate performance in a learning (but not in a recall) situation. Thus, for the present, it can only be tentatively suggested that there may be an inhibitory effect of 8-azaguanine on memory in the psychological sense and that this effect may depend on the incorporation of 8-azaguanine into brain RNA. However, as noted previously, there appears to be an intimate relationship between RNA metabolism and certain other adaptive processes. CREASER[12] has suggested that there are two general types of RNA: (a) that which is necessary for "constitutive" (i.e., normally present) functions and has a slower turnover rate, and (b) that which is necessary for "adaptive" (i.e., arising as a result of a cell's experience with its environment) functions and has a faster turnover rate. One would

expect memory, if it is linked to RNA metabolism, to involve the faster turning over, "adaptive", RNA. Brain RNA might also be capable of "type" changes, thereby allowing strongly reinforced or habitually used memory traces to become "constitutive", and thus achieve a greater degree of permanence.

The present hypothesis and experimental data represent only a rudimentary beginning in the search for a biochemical basis of memory. The present set of experiments does not put the hypothesis to a critical test, although the data are consonant with the hypothesis. Further experimentation on the effect of other inhibitors of normal RNA metabolism (such as other purine and pyrimidine analogues) on the process of memory would certainly be of much interest. The present approach to the problem possibly may provide a useful framework for design of such experiments. Further investigation of the problem of the biochemical basis of memory should shed much light on the manner in which the brain produces adaptive behavior, for the ability to store information from the environment is necessary if the organism is to respond adaptively to the environment.

VOL.
1
1962/

SUMMARY

A hypothesis for the biochemical basis of memory is developed. It is postulated that memory traces in the nervous system are produced by the formation of altered RNA molecules. Data are presented which indicate that 8-azaguanine-2-C^{14} is incorporated into rat brain RNA, and that intracisternally injected 8-azaguanine, while it does not depress a rat's ability to perform and recall a previously well-learned maze, does decrease a rat's ability to learn a new maze. The significance of these results, with respect to the hypothesis cited, is discussed.

Acknowledgements — We wish to express our deep appreciation to Dr. JOHN ROMANO, Dr. GEORGE L. ENGEL and Dr. FRANZ REICHSMAN for their generous advice and support. We would also like to thank Dr. ROBERT ADER for his extensive help in designing the maze experiments, Dr. CHRISTIAN BEELS for help with the statistics, and Miss AILENE WILLIAMS for technical assistance. One of us (M. B. S.) is greatly indebted to Dr. W. ROSS ASHBY for a year of devoted teaching and for many stimulating discussions of the problem of memory.

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OL.
1
62/63

MODIFICATION OF AFFECT, SOCIAL BEHAVIOR AND PERFORMANCE BY SLEEP DEPRIVATION AND DRUGS

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VOL. 1 1962

INTRODUCTION

THE FIRST attempt to study the behavioral reactions of men to sleep deprivation was made by PATRICK and GILBERT[1] more than 60 years ago. These experimenters and those who have followed have concentrated their attention upon the performance of individual subjects on a wide variety of psychomotor, learning, intelligence, coordination, and vigilance tasks. Several reviews of this work are available (BARTLEY and CHUTE[2]; KLEITMAN[3]; WILLIAMS, LUBIN and GOODNOW[4]).

The research reported here departed from this tradition in two ways. It focused on variables related to affect or emotion and it studied these variables in persons working as members of small groups.

CARMICHAEL, KENNEDY and MEAD[5] performed the only experiment immediately relevant to this one. Although primarily interested in the effects of 50 hr of sleep deprivation on some individual performance measures, they also evinced a definite interest in social changes:

"An attempt was made to measure changes in group morale by observing behavior during card games scheduled at three stages of the three day period. . . . Activity, talkativeness and sociability declined during the first 24 hr. The second card game [approximately 30 hr after the three subjects had last slept] was done quietly and without much interest. Social communication dwindled still more after this second game. A game scheduled for Sunday morning was cancelled because the subjects seemed so unresponsive. No important signs of irritability or discontent were observed." (CARMICHAEL *et al.*[5]).

This apparently represents the only previous attempt to assess the effects of sleep

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deprivation upon the behavior of men in a small group situation. Small groups have also rarely been used to study the effects of drugs, the exception here being the work of Wendt's group at Rochester[6–8].

The present report describes the effects of a relatively short period of sleep deprivation — approximately 37 hr — upon the affective responses, social behavior and both group and individual performance of men engaged in standardized activity as members of small groups. It deals concurrently with the effects of a combination of amphetamine sulfate and secobarbital sodium upon these responses in sleep deprived and non-sleep deprived subjects. Other work had indicated that this combination might effectively counteract some of the effects of sleep loss[7–9].

METHOD

Subjects

OL.
1
62/63

The subjects were sixteen undergraduate men at the University of Rochester who were paid to take part. They ranged in age from 19 to 27, with a median of 21 years. Their weights ranged from 145 to 205, with a median of 170 lbs. They were assigned to four four-man groups, with men known to be close friends placed in different groups in order to make groups more homogeneous.

Experimental treatments

1. *Sleep deprivation.* Two levels of sleep deprivation were used. Under the "non-sleep deprivation" treatment, the subjects slept as usual the night before the day of the experimental group session. These sessions occurred in the evening, subjects reporting to the laboratory at 19.00 hr. Under the "sleep deprivation" treatment, they had been denied their sleep, remaining in the custody of an experimenter the previous night. During this time they studied, read, listened to records, played cards or talked to one another. At approximately 07.30 hr these sleep deprived subjects were allowed to leave the laboratory and go through their usual school day. An effort was made to stress the importance of reporting any involuntary naps. A few subjects reported short blackouts during morning lectures, and one reported being awakened by his roommate after he had apparently dozed off for about half-an-hour in the late morning. These lapses seem unimportant since it was not our purpose to study the effects of a deprivation period specified to the minute. At 19.00 hr the subjects returned to the laboratory to start the evening activities. Since the group sessions started at approximately 21.00 hr the men had been awake about 13 hr when they started the non-sleep deprivation sessions and about 37 hr when they started the sleep deprivation sessions.

2. *Medication.* If a "medication" session was to follow, the four subjects in a group were given 10 mg amphetamine sulfate 2 hr prior to the session and 100 mg secobarbital sodium 15 min later. Similar capsules containing only lactose were given if a "non-medication" session was scheduled. Both subjects and observers were unaware of the contents of any given capsule, and subjects were unaware of the drugs under study.

Design

Each of the four four-man groups met six times, two to seven days apart. At the first two meetings the procedure was explained and the self-report instruments administered.

Each group had about 20 min practice on each performance task later used. The amphetamine-secobarbital combination was given at both preliminary meetings. These sessions helped the relationships among subjects to stabilize. No data were collected during them.

During the next four meetings, each group met once under each of the following treatment combinations: (1) non-sleep deprived and non-medicated; (2) sleep deprived and non-medicated; (3) non-sleep deprived and medicated; (4) sleep deprived and medicated. Each group experienced these four in a different sequence, with the four sequences forming a systematic Latin square. A design described by BUGELSKI[10] (Table 1) was used so that

TABLE 1. DESIGN OF EXPERIMENT

	Session 1	Session 2	Session 3	Session 4
Group 1	NSD, M	SD, M	NSD, NM	SD, NM
Group 2	SD, M	SD, NM	NSD, M	NSD, NM
Group 3	NSD, NM	NSD, M	SD, NM	SD, M
Group 4	SD, NM	NSD, NM	SD, M	NSD, M

NSD, NM: non-sleep deprivation, non-medication
SD, NM: sleep deprivation, non-medication
NSD, M: non-sleep deprivation, medication
SD, M: sleep deprivation, medication

as well as each treatment combination appearing only once in each of the four ordinal positions, each appeared only once preceding and only once following each other treatment combination.

Procedure

The four subjects comprising one group arrived at the laboratory at 19.00 hr (Fig. 1). They filled out Adjective Check List I (all instruments will be described in the next section; the three administrations of the Adjective Check List will be designated by Roman numerals). They were then given the first half of the drug combination. Fifteen minutes later the second drug was given. A Sleep questionnaire and a free period followed. A 55-minute long projective test battery was then administered. This consisted of the McClelland Need Achievement Pictures and the Rosenzweig Picture-Frustration Study. Its results are reported elsewhere[11]. The experimental group session started 2 or 3 min after the projective tests were completed. In order to minimize contact between subjects and experimenter, task materials and instructions were placed in envelopes, arranged in the desired order and left in the room with the subjects. The experimenter sounded a buzzer whenever he wanted subjects to stop what they were doing and open the next envelope.

During each of their group sessions the subjects worked on three group tasks:

1. *The ball and spiral task** lasted 12 min (Fig. 2). The men attempted to roll a ball as

* The prototype of the present apparatus originally appears in the psychological literature in a study by FRENCH[12]. The particular version used here was developed by CARTER, HAYTHORN and HOWELL[13].

far as possible up a 4½-turn spiral plane. The spiral was mounted on a 3 ft by 3 ft board, with handles, diagonal to the square, extending outward at the corners. Each subject manipulated one of these while the group attempted to roll the ball up the spiral ramp.

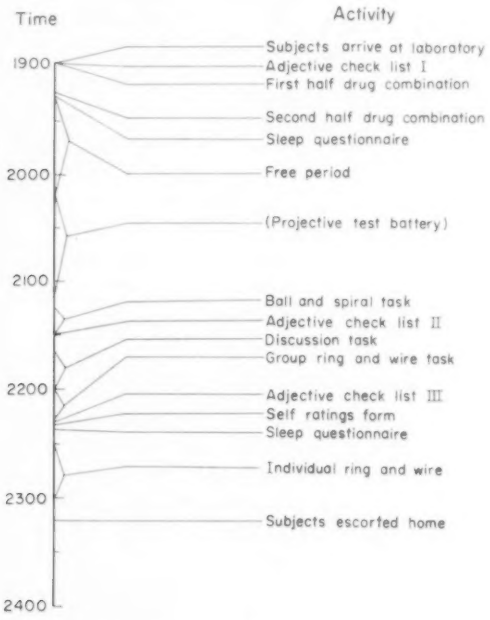

FIG. 1. Log of activities during a typical evening.

The exact instructions were: "Your task here is to run the ball up the spiral track as far as possible. Your score for each time is the point at which the ball falls off the spiral. [Numbers from 1 to 23 were inscribed along the path.] Getting it into the hole on top, however, gives you 50 points. Your score for the session will be the average of the scores attained on the individual attempts." A group member recorded scores on a blackboard.

The buzzer that signalled the end of the Ball and Spiral Task also notified the subjects that they were to fill out Adjective Check List II.

2. *The discussion task*. After subjects had completed Adjective Check List II the buzzer was sounded again, directing them to open an envelope which posed the particular problem they were to discuss for the next 20 min. Four controversial topics were used: the propositions that fraternities are a bad influence on a college campus; that mercy killing should be legalized; that the church as an institution is outdated and serves no useful function in modern society; and how best to handle Communists in America. Each group discussed each of the topics once, and each topic appeared only once under each treatment combination.

3. *The group ring and wire task*. After 20 min of discussion the buzzer sounded to start the subjects on the Group Ring and Wire Task (Fig. 3). An irregularly bent length

of $\frac{3}{16}$ in. diameter wire ran from one side to the other of a 2 ft by 2 ft circular hole in a square 3 ft by 3 ft board. Handles diagonal to the square extended outward at the corners. A loop of $\frac{3}{16}$ in. wire, with an inner diameter of $\frac{7}{8}$ in., encircled the wire attached to the square frame. This loop was mounted on a stand so that it stood 3 ft 10 in. high. The group members were stationed at the four corners. They were instructed: "Your job here is to move the wire through the ring as quickly and with as little contact with the ring as possible." Each traversal from one side of the circular opening to the other was called a "run." These were counted by the experimenter, who was stationed behind a one-way vision mirror. Each contact of wire to ring activated a buzzer that could be heard by the subjects as well as a counter outside their room. The subjects worked on this task for 12 min. A series of forms, including Adjective Check List III, another Sleep questionnaire, and some self ratings along other dimensions were then filled out.

Individual ring and wire task. After the forms were completed, the men were taken individually to another room for the Individual ring and wire task. This was a miniature model of the group task. An irregularly bent wire ran from one side to the other of a 12 in. circular opening centered on a $16\frac{3}{4}$ in. square of $\frac{1}{2}$ in. plywood. A $\frac{5}{8}$ in. ring looped around the wire and was mounted in a stand. The subject grasped the frame as he stood before the apparatus. As on the group task, he moved the bent wire through the stationary ring, from one side of the opening to the other, and back again as quickly and with as little contact of wire to ring as possible. A buzzer sounded while contact was made. One four-minute trial was run. A counter totaled the number of contacts made during that time. The number of traversals or runs across the opening was also counted.

VOL.
1
1962/

Measuring instruments

1. *Sleepiness questionnaire.* Subjects answered the question "How sleepy are you?" shortly after arriving at the laboratory and at the conclusion of the night's session. A nine-point scale was used, five of the points being labeled. The labeling definitions were: 1 — Not at all; I feel quite energetic; 3 — Comfortably relaxed; I could go to sleep easily; 5 — So drowsy that I would like to go to sleep now if I could; 7 — Painfully sleepy; I want to go to sleep now; and 9 — Unbearably sleepy; I can barely stay awake.

2. *Adjective check list.* Subjects checked those adjectives out of a list of 145 that they thought applied to them at the three times already indicated during each evening in the laboratory.* Primarily on the basis of an analysis of the degree to which the various words correlated with each other when checked by other subjects whose mood was varied through the use of drugs, a number of indices had been formed from this list[9, 15]. The score for an index was the total number of adjectives checked, with the exception that for the two indices that contained both positive and negative terms, a point was subtracted for each negative adjective checked. The particular indices used were — *Friendliness–Hostile Aggression:* positive adjectives were adaptable, amiable, cooperative, friendly, generous, genial, kindly, sociable, trustful; negative adjectives were annoyed, argumentative, belligerent, critical, defiant, hostile, irritable, quarrelsome, sarcastic, suspicious; *Task Involve-*

* The rationale behind the use of such a check list has been outlined elsewhere[14].

OL.
1
62/63

FIG. 2. Ball and Spiral Task.

FIG. 3. Group Ring and Wire Task.

VOL.
1
1962/

ment: businesslike, diligent, hard working, industrious, intent, task-involved, work-oriented; *Social Initiative:* adventurous, ambitious, confident, courageous, earnest, energetic, enterprising, exultant, fearless, forceful, indomitable, original, resourceful, romantic, self-confident, talkative, vigorous; *Elation–Depression:* positive adjectives were amused, carefree, cheerful, elated, expansive, expressive, humorous, joyous, warmhearted, witty; negative adjectives were depressed, discouraged, gloomy, glum.

Coefficient Alpha (CRONBACH[16]) was calculated to measure the reliability of the Adjective Check List indices. These coefficients ranged from 0·87 to 0·94. These are estimates, from a single administration of an index, of how highly two such administrations would correlate if it were possible to give the two at the same instant. The appropriateness of this measure for this type of data has been pointed out by Cronbach.

3. *Self ratings.* At the end of each group session, after completing Adjective Check List III, the subjects rated themselves on a number of characteristics, each defined by a different triad of adjectives. A zero ("not at all") to four ("very much") scale was used. On *a priori* grounds several indices were constructed from these. One labeled Friendliness–Hostile aggression, consisted of the mean of the ratings made on dimensions specified by the following three triads of adjectives: adaptable–cooperative–easygoing, obstructive–reserved–suspicious, and annoyed–argumentative–irritable. Its reliability was estimated in the same way as was that of the Adjective Check Lists; Cronbach's Coefficient Alpha was 0·86. Indices for Elation–Depression and Social Initiative proved too unreliable for further consideration. A single triad, task-involved–intent–businesslike, was used to give another measure of Task Involvement. Since only one triad was used, no reliability coefficient can be quoted.

4. *Social behavior ratings.* In addition to the above measures of affect, a measure was obtained of the overt behavior of the subjects as they interacted while performing the group tasks. This was done in the following way. Four observers sat behind a one-way vision mirror which stretched across one side of the experimental room. Each observer watched two of the four subjects for a two-minute period, the end of which was marked by an automatic chime. He then rated them on six dimensions on a prepared form. He switched next to the other two subjects for the next two minutes. Since it took approximately 20 sec to rate, the actual time spent in observation (after the first period) was somewhat less than 2 min. The observers alternated between the two pairs of subjects throughout the duration of the session. Thus, at any point in time, two observers would be watching one pair of subjects while the other two were occupied with the other pair.

The composition of the rating pairs was varied in an unsystematic manner from session to session, each rater being paired with every other approximately an equal number of times. All ratings were made along a five-point scale, with zero representing the minimum and four the maximum score assignable. The raters were professional psychologists, and all had experience in rating the behavior of men working together in small groups. They also had been given practice on the particular rating scales used here in a pilot study, during which they had rated behavior during twelve 40-minute group sessions[9].

The dimensions along which ratings were made were "Hostile Aggression", "Task Involvement", "Social Initiative", "Elation", "Anxiety" and "Cooperation-and-Solidarity". Extended definitions of points along the rating scales for each of these are given elsewhere[17].

Mean product–moment correlations were computed, using session totals for each observer as entries and Fisher's r–z transformation before pooling. The Spearman–Brown Prophecy formula was used to predict the inter-observer reliability of the ratings as they actually were used, since a mean rating from the work of all four observers was used in later statistical analysis[18]. The resulting correlations ranged from 0·81 to 0·94, except for those for Anxiety and Cooperation-and-Solidarity. The latter were too low to allow further consideration of data collected on those dimensions.

RESULTS

Since the subjects worked together and conversed with one another their responses cannot be considered independent. Therefore, each four-man group was considered as a unit in the analyses to be presented. The sole exception to this procedure was made for the data from the Individual Ring and Wire Task, where subjects were studied singly.

Analyses of variance were performed to estimate the reliability of the differences attributable to the independent variables. When the interaction proved significant at the 0·05 level, the appropriate *t*-tests were carried out[19].

Affect

Information about the subjective experiences of the group members comes mostly from the repeated administrations of the Adjective Check List. Fig. 4 summarizes these data, as well as the data drawn from the Sleepiness questionnaire. The range of possible scores varies with the index; these ranges have been indicated on the ordinate.

With a few exceptions, a consistent picture of affect change emerges. It can be summarized quite briefly: (1) Sleep deprivation generally made subjects more "negative" in mood (i.e., they were less friendly, showed less social initiative); (2) the amphetamine–secobarbital combination generally produced more "positive" affect, both when subjects had been sleep deprived and under the control condition; and (3) the drug effect was usually more pronounced in sleep-deprived subjects, wiping out any effects of the deprivation. These statements will be qualified in the following paragraphs, which present the results in detail.

1. *Sleepiness.* Sleep deprivation made subjects more sleepy — a hardly surprising finding (Fig. 4). They were queried twice during the evening; at both times the sleep deprivation effect proved significant.* The drug combination significantly decreased sleepiness.

Note that the mean response of subjects *not* deprived of sleep was 2·4 at the beginning of the evening. When they received only placebos it rose to 3·1 near the end. The statement associated with a rating of three is "Comfortably relaxed; could go to sleep easily". It seems clear that the treatment level labeled "non-sleep deprivation" is far from the zero point when subjective reports of sleepiness are considered.

2. *Friendliness–hostile aggression.* Sleep-deprived subjects reported themselves as significantly less friendly (or more hostile) upon arriving at the laboratory than did non-sleep-deprived subjects (Fig. 4). On non-medication evenings this difference seemed to remain throughout the evening, although sleep deprivation did not achieve significance on Adjective Check List II, filled out part way through the group session, or on Adjective

* The word *significant* will be used to indicate statistical significance at or beyond the 0·05 level.

VOL. 1 1962/

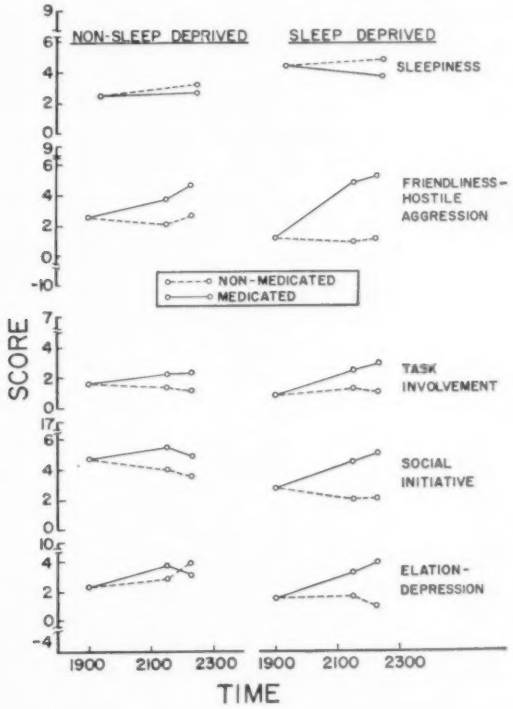

FIG. 4. Scores for various measures of affect as a function of sleep deprivation and medication. All but the Sleepiness score were derived from three administrations of an Adjective Check List (see text). The drugs were administered at 19·05 (10 mg amphetamine sulfate) and 19·20 (100 mg secobarbital sodium). The values derived from Adjective Check List I, given before the drugs were administered, represent the means of all data taken under the indicated sleep deprivation treatment. The drug variable is irrelevant at this time. The range of possible scores is indicated on the ordinate for each measure.

Check List III, filled out at its end. The drug combination made subjects significantly more friendly. This was shown on both check lists administered after the medication. The effect was perhaps more pronounced on sleep-deprived subjects. This is suggested both by the Adjective Check Lists and by the Self Ratings made at the end of the group session. On the latter there was a significant interaction between the two main variables. The mean ratings were: non-sleep deprived, non-medicated 1·5; non-sleep deprived, medicated 1·4; sleep deprived, non-medicated −0·4; and sleep deprived, medicated 2·1. (The higher the score, the more the friendliness.) A t test of the difference between non-sleep deprived, non-medicated and sleep deprived, non-medicated scores showed that the decrease was significant. Taken together, these analyses indicate that sleep deprivation made subjects more hostile so long as they had been given no medication.

3. *Task involvement.* A significant decrease in subjective task involvement following sleep deprivation was present when subjects first came to the laboratory, before they had

had a chance to interact with one another (Fig. 4). The decrease was no longer present on the next two check lists. This suggests that interaction among group members itself served as an effective counterweight to the drop in motivation that followed sleep loss.

The drug combination increased task involvement significantly regardless of sleep deprivation level. The Self Ratings, made at the same time as the last check list was filled out, showed the same effect that was apparent on the check list. The mean ratings were: non-sleep deprived, non-medicated 1·6; non-sleep deprived, medicated 2·1; sleep deprived, non-medicated 1·4; and sleep deprived, medicated 2·4. (The higher the score, the more the task involvement.) Analysis showed that only the effect of medication was significant.

4. *Social initiative.* Upon arriving at the laboratory subjects reported significantly less social initiative on Adjective Check List I if they had been deprived of sleep than if they had not (Fig. 4). A similar difference was again significant for the list filled out immediately after the Ball and Spiral Task. If the subjects had received drugs, these effects of sleep loss disappeared. Thus, on Adjective Check List II, they reported about as much social initiative when both sleep deprived and medicated as when neither. On that check list medication was significant. The interaction between sleep deprivation and medication was not. On the final check list of the evening the interaction was significant. Viewing this interaction from the standpoint of the drugs, it means that they led to a greater change in sleep deprived than in non-sleep deprived subjects; from the standpoint of the sleep variable, sleep loss led to a significant decrease in social initiative only if subjects had not received the drugs.

5. *Elation–depression.* The men reported to the laboratory slightly but not significantly less elated (or more depressed) when sleep deprived (Fig. 4). Nor did any effect of sleep loss appear on Adjective Check List II. At this point the drug combination had produced a significant increase in elation. At the end of the group session, when the third check list

TABLE 2. SOCIAL BEHAVIOR RATINGS

	Non-sleep deprivation		Sleep deprivation			
	Non-medication	Medication	Non-medication	Medication	SD–NSD	M–NM
Hostile aggression	0·17	0·20	0·26	0·26	0·08	0·02
Task involvement	2·63	2·80	2·53	2·53	−0·19*	0·09
Social initiative	2·32	2·42	2·23	2·24	−0·13*	0·05
Elation	1·56	0·95	1·14	0·83	−0·26*	−0·46*

* $p<0·05$

SD–NSD = differences between the means of sleep deprivation and non-sleep deprivation treatments, disregarding medication level.

M–NM = differences between the means of medication and non-medication treatments, disregarding sleep deprivation level.

(The interaction between sleep deprivation and medication was never significant.)

VOL. 1 1962/

was filled out, the interaction between sleep deprivation and medication was significant. At this time subjects were reporting significantly less elation if sleep deprived than if not, provided that no medication was involved. The drug combination significantly increased elation when subjects were sleep deprived, bringing them back to the level shown under non-sleep deprived conditions.

Social Behavior

The preceding paragraphs recounted what subjects themselves reported. Table 2 summarizes the ratings made by the four observers seated behind the one-way vision mirror during the group sessions.

Sleep deprivation led to a slight, but far from significant, increase in Hostile Aggression. It did produce significant decreases in Task Involvement, Social Initiative and Elation. Only the Elation scores were moved to a significant extent by the drug combination; it decreased Elation. All changes were very small.

Performance

The performance tasks were all "self-paced"; i.e., the rate of work was set by the group or individual. On the Ball and Spiral Task, groups worked under instructions that

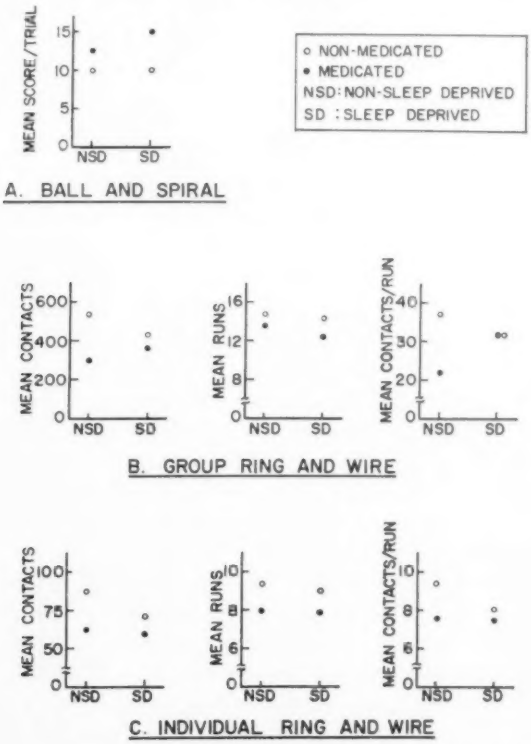

FIG. 5. Performance task scores as a function of sleep deprivation and medication.

emphasized attaining the highest possible mean score per trial during the 12-minute work period. Such a score was computed for each period. The means of these for each of the four treatment combinations are plotted in Fig. 5a. Sleep deprivation had no effect upon this score. The medication increased it to a significant extent. The interaction was not significant.

The instructions for both the Group and Individual Ring and Wire Tasks stressed speed and accuracy equally. Three scores for each task are given in Figs. 5b and 5c — (1) the mean number of contacts; (2) the mean number of runs (traversals of ring from one end of the wire to the other); and (3) the mean number of contacts per run. Sleep deprivation produced no significant effects on any measure for either task. On the Group Ring and Wire Task, *t* tests of the sleep deprivation-induced changes were made after a significant interaction was found in the mean contacts per run. None was significant.

The medication was a more potent variable. On the Group Ring and Wire Task subjects made significantly fewer contacts of wire to ring when they had been given the drug combination. A like decrease was shown on the Individual Ring and Wire Task. Again the change was significant. The number of runs also decreased on both group and individual tasks. But the drop was not significant on the former while it was on the latter. The derived measure of mean contacts per run also showed medication-induced decreases for both tasks. This drop was not significant on the individual task. On the group task the decrease occurred only when the groups had not been deprived of sleep. The significant interaction between sleep deprivation and the drug combination was probably the product of this differential effect.

VOL.
1
1962

DISCUSSION

A short sleep deprivation period led to reliable changes in how men working in small groups felt and how they acted. The shifts were toward the negative end of most of the dimensions studied. Compared to their non-sleep deprivation control data, subjects entered the laboratory reporting less friendliness, less task involvement, and less social initiative. At the end of the group activities, friendliness and social initiative remained low but the task involvement had increased to its control level. The subjective reports of elation started at about the control level and decreased until they were significantly lower at the end of the group session. Observers seated behind a one-way vision mirror rated the subjects as lower in task involvement, social initiative, and elation during the group session that was run after sleep deprivation than during the similar session run without loss of sleep. An interesting exception to this negative picture occurred with overt hostile aggression, where the amount seen by observers did not change with sleep deprivation. Neither group nor individual performance scores changed with sleep loss.

The amphetamine–secobarbital combination led to reports of more positive affect but did not greatly alter overt social behavior. Subjective friendliness, task involvement, social initiative and elation were all reported increased by the drug combination. The increase was greater for sleep deprived subjects than for those allowed a normal night's sleep. Overt behavior did not change under medication save for a decrease in the elation score. Subjects working under medication did better on both group and individual performance tasks.

Others have also reported changes in both affect and overt behavior after sleep deprivation. But almost all of them reported the changes in anecdotal terms and rarely specified at what point during the deprivation period particular incidents occurred. Nevertheless, it seems clear that the increase in verbal reports of hostile aggression is another instance of one of the most often cited products of sleep loss[20]. At the same time the lack of an increase in observable aggressive behavior confirms the observation of CARMICHAEL, KENNEDY and MEAD[5] quoted above.

The relation between what sleep deprived subjects report about their relative friendliness and what they display to the eyes of observers is not a direct one. Perhaps the difference reflects a long history of social learning: hostile affect is not often punished while hostile behavior often is. Perhaps it also reflects pressures arising within the small group itself. Two of the three group tasks demanded cooperative activity; high scores reinforced cooperation. Any display of hostility placed the group goal of good performance in jeopardy. Thus, one might expect that overt friendly, cooperative behavior would be maintained even in the face of rising covert antagonisms. In fact, cooperation does sometimes increase under stress. LANZETTA[21] studied group members working under a time stress with the experimenter continually badgering them and belittling their performance. He concluded that "under increased stress members of a group show more behavior which tends to reduce interpersonal tension and friction and less behavior which might lead to increased disharmony. They will become less argumentative and aggressive, and more cooperative and friendly."

Another common report from previous work is that sleep deprived subjects show decreased motivation. Inability to concentrate, inattention and a general unresponsiveness are often cited[1, 5, 22, 23]. As with aggression, the nature of the change depended upon the circumstances at the moment of measurement. At the beginning of the evening, the subjects reported less task involvement when sleep deprived than when not so deprived. But the difference disappeared on the measures taken during and after the group session. This suggests that working together as a group greatly modified this particular subjective reaction to sleep deprivation.

The drug combination produced a uniformly positive picture on the measures of affect but changed only one social behavior measure significantly: elation decreased. LANZETTA, WENDT, LANGHAM and HAEFNER[7] also found only partial agreement between measures of mood and behavior when they were examining the effects of this same drug combination. Their subjects worked in three-man groups on a task that they thought was part of an evaluation of them that was to become a part of their permanent military reserve training record. Under this stress, medicated subjects checked more adjectives (on a check list similar to the one used in the present study) that connoted "a relaxed, positively affective, cooperative, phenomenal state," while they checked fewer adjectives that connoted "an anxious, obstructive state". Observer ratings of aggression, cooperation, sociability, self-orientedness, and six other dimensions showed no significant differences attributable to the drugs. However, a behavior interaction category system also used by observers did show significant decreases in tension and tension release, disagreements and antagonisms.

The group performance tasks remained unchanged after the short period of sleep deprivation. The drug combination led to superior performance on both the Ball and

Spiral and the Group Ring and Wire tasks by most criteria. How were these effects mediated? Do they reflect variations in interpersonal affect and thus changes in the ease with which group members worked with one another? PAYNE and HAUTY[24] have pointed out that subjective predispositions are frequently invoked to account for changes in the task proficiency of individuals working alone. They measured performance with a complex compensatory pursuit task and predispositions with a questionnaire. By varying drug treatment and instructions they succeeded in inducing differing attitudes toward the task. Their performance measure was moved only by the drugs. After a detailed analysis, in which they adjusted the performance scores for their regression upon the task-attitude scores and still found significant drug variation remaining, they state that these drug effects on performance "could only slightly, if at all, be accounted for by subjective effects". They concluded that their results "tend to discredit the general practice of invoking attitudinal constructs to explain work-decrement phenomena in the absence of confirming experimental demonstrations".

The present experiment fails to demonstrate any consistent effect of variation in the mood of group members on group performance. What subjects reported they felt and how well they performed on group tasks seem to have varied independently. Increased positive affect, induced by the drug combination, was indeed accompanied by better group performance. But the increased negative affect induced by sleep deprivation was not associated with poorer performance. And the individual task served in part as a control procedure: the fact that subjects performed both the group and individual tasks better when they had had the drugs argues against the notion that the group change was mediated by any process peculiar to the group situation.

VOL.
1
1962/

SUMMARY

A 37-hour period of sleep deprivation proved sufficient to induce reliable changes in how men working together in small groups felt and how they acted. These changes generally reflected both more negative affect and more negative behavior. However, while verbal reports of hostility increased, overt aggressive behavior did not. The subjects worked on both group and individual performance tasks, none of which showed effects of sleep loss.

A combination of amphetamine and secobarbital moved reports of affect in a "positive" direction, with effects usually greater with sleep deprived subjects. Task performance was improved by the drugs while overt social behavior usually was unchanged.

No evidence was found that the group performance changes were mediated by changes in interpersonal affect.

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OL.
1
62/63

SEX DISTRIBUTION AND THE SEVERITY OF ILLNESS AMONG SAMPLES OF SCHIZOPHRENIC TWINS

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VOL.
1
1962/

IT IS not unusual for knowledge to be advanced by an effort to understand what underlies a found difference which is unexpected, even if the difference is small. In those fields concerned with the psychiatric disorders, it is often said that schizophrenia probably occurs as frequently in one sex as the other, yet if one examines the five major twin studies of schizophrenia[1–5] one finds an excess of females over males among the total of twin index cases in the combined samples, the excess occurring in the three largest of the five studies (Table 1).

TABLE 1. SEX DISTRIBUTION AMONG TWIN INDEX CASES WITH A DIAGNOSIS OF SCHIZOPHRENIA

	Total		MZ		DZ	
	♂	♀	♂	♀	♂	♀
Luxenburger (1928)*	32	33	9	8	18	15
Essen-Möller (1941)†	18	14	3	4	15	10
Rosanoff (1934)†	51	86	19	22	32	64
Kallmann (1946)	439	514	121	147	318	367
Slater (1953)*	54	104	12	29	40	75
Total	594	751	164	210	423	531
Per cent	44·2	55·8	43·85	56·15	44·3	55·7

* In the Luxenburger study, ovularity was uncertain in 15 same-sex pairs of whom 5 were male, 10 female. In the Slater study, 2 pairs were of doubtful ovularity.

† In the Essen-Möller study, the sex of the index case in 37 opposite-sex pairs is not stated. In the Rosanoff study, the sex of the index case in 5 opposite-sex pairs is not stated. These pairs are excluded from Table 1.

In Table 1, female patients constituted 55·8 per cent of all the twins sampled, 56·15 per cent of all the monozygotic (MZ) twins, and 55·7 per cent of all the dizygotic (DZ) twins. If one assumes a theoretical expectancy of half male and half female for the total sample

as well as for the MZ and DZ twins, then the observed discrepancies from this expectancy are all statistically significant. Chi-square equals 18·33, 5·66 and 12·23 for the total, MZ and DZ groups, P being less than 0·001, 0·02 and 0·001 for the three groups respectively.

Our inquiry aims to determine why this difference occurs. It should be said at the outset that an excess of female over male twins has been reported in nonpathological samples. For example, Wilson and Jones[6] report six studies[6–11] which attempted to obtain representative samples of school-age twins in California, Wisconsin, Canada, Germany and Sweden. Counting only same-sex pairs, there was an excess of girls over boys in each study. Sometimes the difference was slight, sometimes large. For all six studies, male pairs constituted 43·8 per cent and female pairs 56·2 per cent of the total sample, figures which correspond closely to those of Table 1. Wilson and Jones believed that the excess was caused by a higher mortality among male than female twins.

This explanation is questionable, however, since there is an excess of same sex male as compared to same-sex female twin pairs at birth. Wilson and Jones cite figures obtained in the first quarter of this century from the U.S.A. and various European countries which show that of all same-sex twin births, 51·6 per cent were male and 48·4 per cent were female. These figures were quite consistent from country to country. In the U.S.A., 813 of 1,000 single-born males and 838 of 1,000 single-born females were still alive at age ten, according to the 1910 census[12]. If we estimate that the relative proportion of male to female twin survivors is approximately the square of the proportion for single-borns, then 661 of 1,000 male twins and 702 of 1,000 female twins would survive to age 10. Since of all twins born, 51·6 per cent were male and 48·4 per cent female, then at age ten there would have been 341 male twins to 340 female twins in the population.*

It is not easy to explain the higher proportion of female twins in the six studies of school-age twins, if the above estimate of the sex distribution among twins is correct. One could only suppose that some aspect of the sampling procedures used had suppressed the reporting of male twins among same-sexed pairs. Similarly, one could hypothesize that the high proportion of female to male twins with schizophrenia also resulted from some systematic sampling bias.

Before exploring the tenability of this hypothesis, we should recognize the possibility of two alternatives — 1. Female twins may actually be more susceptible to schizophrenia than male twins. 2. Schizophrenia may occur more frequently among females than males generally, the higher incidence among female twins merely reflecting this more general sex difference.

The first alternative will be considered later. Evidence with respect to the relative incidence of schizophrenia in males and females is available for hospitalized cases. Since all the twin samples in Table 1 are from hospitalized cases, such evidence is suitable for our purposes. Figs. 1 and 2 depict the first admission rates by age for both sexes.

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* I wish to thank Dr. Gordon Allen for his help in estimating the male–female twin ratios in the school-age population.

Very recently, J. Yerushalmy, Professor of Biostatistics at the University of California has kindly shown me some data which he has obtained in a large epidemiological study which is not yet published. His figures are in remarkably close agreement with our own estimate, showing almost equal numbers of male and female twins at age five. There were actually a few more males. After age one, there was no sex difference in the mortality of his twins.

Fig. 1 gives the actual number of first admissions for New York State during 1929–1931[13]. Fig. 2 gives the rates per 100,000 population for the United States in 1933[14]. It can be seen that the shapes of the curves are remarkably similar. In the overall, there are more

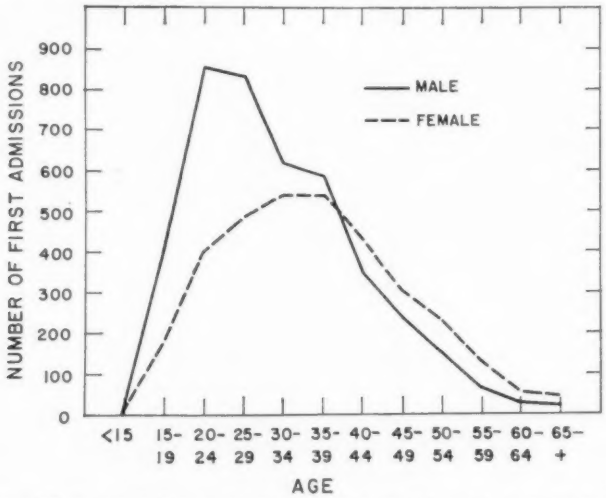

FIG. 1. Number of first admissions for schizophrenia for New York State Mental Hospitals, 1929–1931, by age and sex (MALZBERG[13]).

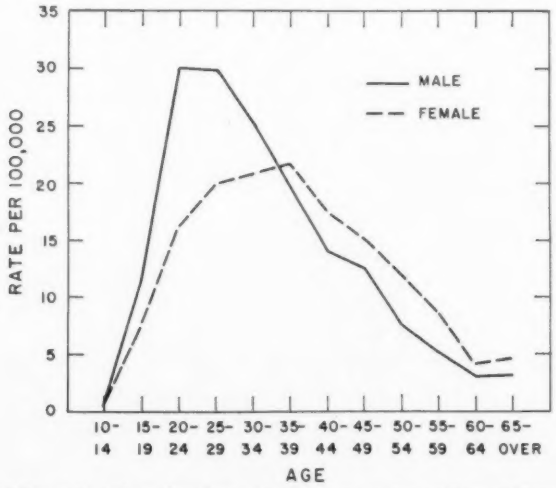

FIG. 2. Number of first admissions for dementia praecox to State Mental Hospitals in the United States, 1933, by age and sex (LANDIS and PAGE[14]).

males than females. During the fiscal year 1932–1933, the excess of male over female admissions in New York was nine per cent[15]. Below age 35, the excess of males was 46·9 per cent. From age 35 and above, the excess of females was 39·1 per cent. Similar

VOL. 1 1962/

admission curves, I believe, obtain today. To compile such curves, however, involves integrating the reports of the military services and the Veterans Administration with those of the public and private hospitals in the United States. This is necessary because so many young males are now admitted to military and veterans' hospitals. It is difficult to do because not all reporting groups use the same age categories and because the Veterans Administration does not report first admissions. However, my own survey of reports during the mid-fifties suggests that if all figures could be combined, similar admission curves would probably still be found.

The main conclusion to be drawn from these data, as far as our own inquiry is concerned, is that females are not more frequently admitted to hospitals with schizophrenia than males. In fact, the reverse seems to be true. If twins do not differ in this respect from single-borns, we should actually expect to find more male than female twins with schizophrenia, in contrast to the sex distribution in the samples of Table 1.

OL.
1
62/63

Let us examine the question of sampling bias. Aside from other differences which are probably of less importance, the five studies may be divided into two groups according to the sampling procedure used. LUXENBURGER[3] and ESSEN-MÖLLER[1] obtained samples derived from consecutive admissions as listed in patient rosters over a number of years. In both studies, the twinship of each admitted patient was determined directly from birth records. Luxenburger also subsequently sampled all patients resident in Bavarian hospitals on a given date, so that his sample consists of two parts which he has not kept separate. Essen-Möller's sample is relatively "pure" with respect to ascertainment of consecutive admissions only. I have described these sampling procedures in greater detail in another paper[16].

The other three studies[4, 5, 17] started with a large resident population in a number of stipulated hospitals to obtain their first group of twins, and then added new cases from subsequent admissions as these were reported by cooperating hospital personnel. Ascertainment of twinship was made from hospital records and by questioning relatives, friends, and the patients themselves.

If we now refer back to Table 1 and consider the male–female proportions in the two groups separately, we find that in the combined samples of Luxenburger and Essen-Möller there are fifty males and forty-seven females. These figures are close to theoretical expectancy. Among the second sampling group we find 544 males and 704 females, so that it is in the samples of cases from large resident populations and twins ascertained through hospital inquiry that we find the excess of female twins. Since Luxenburger also used a resident population as part of his sample, one may question why the excess of females did not occur in his study. One could infer that the part of his sample obtained through strictly consecutive admissions had resulted in an excess of males which cancelled out the excess of females obtained in his resident hospital group. Although Essen-Möller's sample is the smallest, it nevertheless samples most strictly from consecutive admissions, and his proportion of males to females is 56·25 per cent to 43·75 per cent, which accords most closely with the first admissions figures for New York and the United States, as cited above.

If the first alternative hypothesis mentioned above were true, viz., that female twins may actually be more susceptible to schizophrenia than male twins, then we should have found a higher proportion of female index cases in the objectively ascertained samples

obtained by consecutive admissions as well as in the second sampling group. Since we did not, it appears that this hypothesis is not tenable either.

We now need to understand why it is that an excess of female twins occurs when one samples from a large initial resident population and ascertains twins through delegated interviewers, but does not occur when one samples from consecutive admissions and ascertains twinship from birth records. To obtain a possible answer to this question, I have been fortunate in obtaining some unpublished data graciously provided by Dr. FRITZ A. FREYHAN. The data are shown in Table 2.

TABLE 2. HOSPITALIZATION HISTORY OF ALL MALE AND FEMALE PATIENTS ADMITTED TO DELAWARE STATE HOSPITAL, 1900–1950, AND DIAGNOSED SCHIZOPHRENIA
(Courtesy of Dr. Fritz A. Freyhan)

	Male	Female
Total Admissions	740	748
Continuously Hospitalized	258	262
Separated	482	486
Died in Hospital	145	128
Remained Separated	209	190
Readmitted/Rediscarged	131	115
Readmitted/Remained	142	181
Total	482	486

Chi-square = 6·80, $P<0·05$

Delaware State Hospital, in which the data of Table 2 were obtained, is well suited for providing information regarding our inquiry since it is the only psychiatric hospital, public or private, in a well-circumscribed geographic area. All Delaware residents requiring hospitalization are admitted there, and only a small proportion emigrate from the state. The table includes all admissions to the hospital during the first half of this century.

It can be seen that the ratio of male to female admissions was very close to 1:1. The expected excess of males was not found, presumably because since World War II, a number of potential male patients were admitted to military or Veterans Administration hospitals instead. No difference between the sexes existed with respect to continuous hospitalization or separation. Males were, however, more likely to die in the hospital.

It is the lower half of the table which is of particular interest to us. Of all patients discharged, more males than females remained separated. Among all readmissions, more males were redischarged and more females remained in the hospital. The difference between the sexes with respect to getting out again or remaining was statistically significant. With respect to all readmissions who remained in the hospital, 44·0 per cent were male and 56·0 per cent were female. With respect to the combined twin samples starting with large resident populations, 43·6 per cent of the index twin cases were male and 56·4 per cent female.

Thus, there appears to be an association between chronicity of illness and excess of female over male patients in populations of hospitalized schizophrenic patients. This point

may be demonstrated more directly with respect to the twin studies. KALLMANN's first large report was made in 1946[17]. A second report appeared in 1950[14]. The first report included in large part those cases obtained as part of the original survey of hospital residents. Increases in the number of index cases in the second report would represent mainly new admissions between 1946 and 1950. The sex of the index cases obtained by the two sampling procedures is shown in Table 3.

TABLE 3. FREQUENCY OF TWIN INDEX CASES BY SEX USING TWO SAMPLING PROCEDURES
(Data taken from KALLMANN[2, 17])

Sample	Male %	Female %
Cases in 1946 report*	207 (44·0)	263 (56·0)
Cases added between 1946 and 1950	232 (48·0)	251 (52·0)

* Excludes 221 opposite-sex twin pairs in which the sex of the index case was not indicated.

In the 1946 report, male twins constituted 44·0 per cent and female twins 56·0 per cent of all index cases, a difference of twelve per cent which deviated significantly ($P < ·01$) from a 1:1 expectancy. But among new admissions between 1946 and 1950, males constituted 48·0 per cent and females 52·0 per cent of all index cases, a difference of only four per cent which was not significantly different from a 1:1 expectancy. We assume that the slight excess of females in the admissions between 1946 and 1950 was due to a number of potential male patients having been admitted to military or Veterans Administration hospitals. Presumably, this factor was operative to the same extent during the war years, contributing partly to the excess of females in the 1946 report. The significant excess beyond that however was probably due to the initial sampling from a chronic population, this sampling having started before the war in 1936.

If the reasoning thus far is sound, we should be able to make some predictions about the interesting problem: Among twins who are concordant with respect to schizophrenia, which twin becomes the index case? This question has two implications — 1. The twins who get into a sample define and limit the population to which generalizations can be made. 2. Twins who meet the criteria for ascertainment but who are characteristically missed as index cases define the group to whom generalizations cannot be made unless a fresh study is done which aims at their inclusion as index cases.

The prediction of special interest that we can make is that the concordant twin who becomes the index case is the one who is more chronically ill, and, by implication, more severely ill. Slater's published case histories[15] enable us to test this prediction.

For our purposes, we may look only at those concordant pairs who were monozygotic. In Slater's sample there were twenty-four such twin pairs of both sexes. It is most instructive

if we examine separately the group which accords with the prediction, the group which does not, and the group with both twins index cases (four pairs)*.

Of the nineteen pairs in which only one twin was the index case, in twelve instances the twin whose first admission came at the earlier age was the twin who became the index case. The median age at first admission for these twelve index cases was 26 yr and for their cotwins was 38 yr, so that the difference in chronicity for this predicted group was considerable.

By contrast, among the group of four pairs with both twins index cases, the mean intrapair difference regarding age at first admission was about 1·25 years. The maximum difference between members of any pair was two years. Thus, the closer the age at first admission, the more likely were both members of a twin pair to become index cases. This is importantly involved in the calculation of concordance rates and morbidity risks, since each such pair is counted twice. We need to ask if it is reasonable to double the weighting of such pairs relative to other concordant pairs, when the major factor really being weighted is the intrapair difference in age at first hospitalization.

There were seven pairs which did not accord with the prediction in that the twin whose first hospitalization came later was the twin who became the index case. In some respects, this group is the most interesting of all, and the relevant information regarding these pairs has been compiled in Table 4.

TABLE 4. RELEVANT HOSPITALIZATION HISTORY OF PAIRS OF SCHIZOPHRENIC MONOZYGOTIC TWINS IN WHICH THE COTWIN WAS HOSPITALIZED BEFORE THE INDEX CASE
(Data taken from SLATER[51])

Case No.	Age at first Admission		Hospitalization history of the cotwin
	Index case	Cotwin	
4	32	in 20's	Quick recovery, married, no further illness.
8	42	28	Died in M.H. 3 years after admission.
11	29	24	Died 6 months after admission.
43	35	28	Two remissions, whereas index case had uniform progression of the illness.
104	59	39	Died 3 months after admission.
115	25½	25	Discharged after one year. Index case had a downward course of illness.
137	16	14½	Both had repeated discharges and re-admissions.

* Case No. 110, in which only one twin was the index case although both twins were admitted on the same day, is excluded in this analysis since it neither accords with nor goes counter to the prediction.

In three pairs, the earlier admitted twin died relatively shortly after admission. Such cases would be ascertained in a consecutive admissions sample but would be missed if one sampled from a resident population.

In three pairs, the cotwin had a more favorable course of illness. Two of these cotwins were sufficiently recovered to remain out of the hospital. Such cases would also be ascertained in a consecutive admissions sample. Thus, sampling from a resident population increases the likelihood of not including patients with favorable outcomes.

In the seventh pair, both twins were admitted at a very early age, the pattern of repeated discharges and readmissions making it a matter of chance with respect to which twin got into the sample. In such cases chance would be related to the particular time and duration of sampling, whether ascertainment had been through consecutive admissions or through sampling of a resident population.

Thus, the main conclusion of this analysis is that drawing one's index cases from a resident population favors the inclusion of chronically ill patients in the sample and the exclusion of patients with a more favorable course of illness. Twins of the latter type who have cotwins with illnesses at least as favorable are likely to be missed altogether unless sampling is by consecutive admissions.

OL.
1
62/63

DISCUSSION

The implications of the above findings and the inferences based upon them can best be demonstrated by data taken from KALLMANN's 1946 report[17]. These data have been arranged for presentation in Table 5.

TABLE 5. SEVERITY OF THE ILLNESS IN THE MONOZYGOTIC COTWIN IN RELATION TO SEVERITY OF THE ILLNESS IN THE ORIGINALLY ASCERTAINED TWIN
(Data taken from KALLMANN[2])

If severity of the first twin's illness is classified	The severity of the cotwin's illness is classified:				
	Extreme	Medium	Little or no deterioration	No schizophrenia	Total
Extreme	29	10	9	0	48
Medium	0	33	20	0	53
Little or no deterioration	0	0	19	54	73
Total	29	43	48	54	174

Kallmann grouped his cases according to four degrees of severity or deterioration. We are not told how reliably such sortings of cases could be made, but similar kinds of ratings in our own laboratory have been made with high reliability[18]. It is striking that among

the 174 pairs of MZ twins in the sample, there was not a single instance in which the cotwin's illness was more severe than that of the twin originally ascertained. This was also true for all forty-seven concordant DZ pairs. When the first twin's illness was moderate or extreme, concordance was 100 per cent. When schizophrenia in the first twin involved little or no deterioration, concordance was twenty-six per cent.

A previously published analysis of Slater's cases by ROSENTHAL[19] showed similar trends. Male MZ twin index cases who had a more unfavorable social and sexual premorbid history, an earlier onset, and a severer form of illness were more likely to have a concordant twin. Discordance occurred among male pairs where these features of the illness were generally more favourable. Yet there was not one MZ male index case in the sample who had a premorbid history which would have indicated a good prognosis.

Thus, not only do we have rather convincing confirmation of the fact that such sampling procedures favor the inclusion of more severely ill patients, but it also appears that when the more favorable cases are missed, estimates of concordance rates and morbidity risks are misleadingly inflated. A disproportionate overrepresentation of severer MZ cases tends to move the estimate toward complete concordance, while an underrepresentation of less severely ill patients does not permit the full weighting of a group whose concordance rate is twenty-six per cent or less.

When sampling is by consecutive admissions only, with complete ascertainment of twinship, a somewhat different picture from that of Table 5 emerges. For example, in ESSEN-MÖLLER'S series[1] there were seven MZ twin index cases with schizophrenia.* Of the two with nonschizophrenic cotwins, the index case in both instances was said to have a "typical schizophrenia" in which the extent of deterioration would probably be rated in the mild to medium range. Among the five pairs said to be concordant, one index case would probably be rated as having medium deterioration, three medium to severe, and the fifth clearly severe. Yet among their cotwins there was no deterioration at all, complete recovery or personality restoration occurring in four cases, and the fifth showing "mild schizophrenic symptoms without character defect".

Thus, the difference in severity of illness between an index case and his cotwin appears to be considerably greater in samples based on consecutive admissions and when twinship is ascertained from birth records as compared to samples which include resident populations and which are obtained through delegated interviewers. This suggests a corollary inference that discordance rates with respect to schizophrenia itself would be higher in large samples of MZ twins ascertained from strictly consecutive admissions, an inference already implied in our above analysis.

The point could be raised that when one samples from strictly consecutive admissions, one does not allow the cotwin to have passed through the age of risk regarding susceptibility to the illness. Nevertheless, methods for handling this problem exist. KALLMANN[2] has relied on Weinberg's shorter method, and SLATER[5] has devised a method based on correlations among twins with respect to age of onset, to calculate concordance rates for samples which include twin pairs who have not yet passed the risk period.

* Even in Essen-Möller's sample, a source of bias occurred in favor of excluding less severely ill index cases. This resulted from the fact that the birthplace had not been recorded for about 600 cases who "were almost exclusively patients who were mildly ill" and whose twinship therefore could not be ascertained.

VOL. 1 1962/

It could be maintained, too, that if one waited twenty or more years, concordance with respect to severity of the illness in a twin sample obtained through consecutive admissions would be increased. This is possible, but not likely to be significant, since we know that a relationship exists between age of onset and outcome: the later the age of onset, the less likely is the outcome to be deteriorative. LUXENBURGER[3] was the first to note a direct relationship between similarities of twins regarding age of onset and similarities with respect to outcome.

What are the implications of these observations and conclusions for furthering our understanding of the etiology of schizophrenia? If we employ an analysis of variance model in thinking about the etiology of schizophrenia, we want to know how much of the variance is attributable to main genetic and environmental factors under uncontrolled but perhaps specified cultural conditions, and how much is due to first and second order interactions between these main factors. If we were to consider only a sample such as that of Table 5, in which there is almost complete concordance between MZ twins with respect to severity of the illness, we would probably conclude that hereditary factors are accounting for almost all the variance both with respect to the occurrence of schizophrenia and the severity of the illness. If on the other hand we were to consider only a sample like Essen-Möller's, in which there is almost complete discordance in MZ twins with respect to severity of the illness, we would attribute a much greater proportion of the variance to the environment, either in terms of its ability to inhibit phenotypical expression of the illness in gene carriers, or its ability to induce or exacerbate schizophrenic symptoms. In the former case, we would direct all our energies toward discovering the metabolic disturbance for which the inherited allele is responsible. In the latter instance, we would apportion a sizeable share of our energies toward discovering those constitutional and life experience factors which are implicated in the illness either directly or through the mediation of a particular kind of heredity.

OL.
1
62/63

SUMMARY

There is an excess of females over males in twin studies of schizophrenia which have been reported in the literature. Evidence suggests that there are about as many male as female twins in the adult population, and more males than females hospitalized for schizophrenia. Various data indicate that when sampling is based on consecutive admissions and twinship is ascertained from birth records, the excess of females does not occur. When ascertainment depends on delegated interviewers and when one samples from resident hospital populations, the excess of female schizophrenic patients appears. It is shown that excess of females is related to chronicity of the illness in the patient sample.

When the former method of sampling is used, concordance between MZ twins with respect to severity of the illness is much less than when the latter method of sampling is used. The latter method produces data which suggest that hereditary factors account for almost all the variance with respect to the occurrence of schizophrenia or its severity. The method of consecutive admissions, with twinship ascertained from birth records, yields information which suggests that nonhereditary factors are accounting for an appreciable amount of the total variance.

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VOL. 1 1962/

OL.
1
62/63

THE PHYSIOLOGICAL AND PSYCHOLOGICAL EFFECTS OF INTRAVENOUSLY ADMINISTERED EPINEPHRINE AND ITS METABOLISM IN NORMAL AND SCHIZOPHRENIC MEN — I.

EFFECTS ON HEART RATE, BLOOD PRESSURE, BLOOD GLUCOSE CONCENTRATION AND THE ELECTROENCEPHALOGRAM

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THERE are several reasons for the interest in epinephrine which exists among those who have been concerned with the biological causes or correlates of schizophrenia. The relationship between that hormone and various forms of stress, and with affective states such as anxiety, fear and anger, has become increasingly well delineated, while stress itself and its psychological sequelae have been thought of as cardinal features of the schizophrenic illnesses. A number of studies have found a lessened responsiveness to injected epinephrine among some schizophrenic patients in comparison with control groups, especially with respect to its effects on blood pressure, heart rate and blood glucose[1–6]. Within the past decade an hypothesis has been developed which attempts to explain many of the manifestations of schizophrenia on the basis of the accumulation of abnormal and psychotomimetic products resulting from the faulty metabolism of circulating epinephrine[7, 8].

In 1957 the first major metabolite of epinephrine was identified by ARMSTRONG, MCMILLAN and SHAW[9], and in the succeeding three years, AXELROD and his associates in this laboratory[10–14] had delineated the principal pathways in the metabolism of that hormone by lower animals and man and had identified its major and a number of its minor metabolites. This has made possible a study of the metabolism of epinephrine in two carefully selected groups of schizophrenic and normal males[15] and a re-examination of the responsivity of these groups to the intravenous administration of that hormone.

EXPERIMENTAL SUBJECTS AND FACILITIES

Twelve male, chronic schizophrenic patients and thirteen normal male subjects (non-schizophrenic, without "medical" illness) were studied. The criteria on which the schizophrenic patients were selected for hospitalization at this facility have been presented

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elsewhere,[16] as have the general characteristics of the population of volunteers from which these normal subjects were selected[17]. Detailed psychiatric information appears in the second paper of this series.[18]

The two groups of subjects lived in separate but similar patient units, were fed the same regular hospital diet essentially *ad libitum*; coffee and tobacco were unrestricted. Both groups were encouraged to make full use of the available recreational facilities, such as basketball, baseball and table tennis. The range of physical activity among individuals in both groups varied from very active to sedentary, but as a group the normal subjects were

TABLE 1.

		Age	Weight (kg)	Height (cm) / $\sqrt[3]{\text{Weight (kg)}}$	Hospital stay (months)	Smoking (cig./day)	Coffee (cups/day)
SCHIZOPHRENIC PATIENTS	S 5	38	86·9	38·5	12	0	9
	S 4	38	78·2	38·4	12	30	4
	S 1	35	73·5	42·5	13	0	4
	S 6	30	76·9	42·9	13	0	0
	S10	28	119·0	39·9	8	0	1
	S 3	34	94·2	41·0	15	20	1
	S12	41	83·3	40·2	4	0	2
	S 2	31	63·5	44·0	17	20	1
	S 7	37	66·0	42·3	17	40	5
	S11	29	90·0	39·2	11	0	6
	S 9	35	80·4	43·0	12	40	9
	S 8	27	67·0	43·2	19	30	4
	Average ± S.D.	33·6	81·34 15·27	41·26 1·97			
NORMAL SUBJECTS	N14	20	74·7	40·6	3	0	0
	N 3	20	69·5	43·7	3	0	1
	N 6	21	65·5	42·2	1	0	0
	N 1	19	65·1	44·0	1	0	1
	N 7	19	75·0	45·0	2	0	1
	N 5	18	75·1	44·8	2	0	0
	N 4	23	79·1	39·5	6	0	0
	N 2	22	85·0	39·5	7	0	0
	N 8	19	72·5	40·4	2	5	2
	N 9	21	69·2	39·8	2	10	2
	N11	18	72·5	41·7	1	5	3
	N12	21	74·3	44·0	1	0	0
	N10	20	59·4	45·8	1	0	0
	Average ± S.D.	20·1	72·13 6·48	42·38 2·28			

more active, in accord with their age and interests. The difference in physical activity is reflected in average caloric intake, which was approximately 2900 calories per day for schizophrenic patients and 3500 calories per day for normal subjects. Average protein consumption per day of patients was 112 g and of normal volunteers, 145 g. None of the subjects had received drugs in amounts or at times likely to influence the study. Data pertaining to age, weight, use of coffee and tobacco, and duration of stay at the Clinical Center of the National Institutes of Health prior to the study appear in Table 1. It is apparent that the normal subjects generally were younger, lighter in weight (although not significantly so relative to height), used less coffee and tobacco, and had spent less time in the hospital.

The study extended from November 1958 to August 1959. Each subject participated in the procedure once. Schizophrenic and normal subjects were studied alternately and in the same 10 × 18 ft air-conditioned experimental room, which was located in the area where the schizophrenic patients lived. Room temperature was constant within 1°F. during each procedure. The extremes of temperature and wet-bulb relative humidity throughout the study were 77–81°F. and 47–63%.

The procedure room contained several small tables for the equipment needed to prepare infusions and insert needles, an infusion pump of either the Bowman or Harvard design, an infusion stand, various electrodes and lead-wires, two microphones, a large laboratory timing clock, several stools and chairs, and a large metal table covered by a foam-rubber mattress and located near a one-way vision mirror. An oscilloscope was located under the table.

Observers, recording apparatus and aural monitors were in an adjoining room. The observers could see and hear events throughout the procedure. The physician who gave the epinephrine and drew blood samples could hear observers through a small earphone, and watch cardiogram and blood pressure tracings on the oscilloscope. Precise timing of the procedures and continuous assessment of circulatory status were thus insured.

PROCEDURE AND METHODS

Each study was conducted on a Tuesday morning. Normal volunteers were asked several days in advance to participate. The procedure was explained to them both verbally and in a brief written statement, and their signed consent was obtained. This is standard procedure at the Clinical Center and all of the volunteers had signed at least one such statement prior to this one. They were told that the procedure was not particularly hazardous, but that it was lengthy, complicated, tiresome, and sometimes uncomfortable.

The explicit warning and preparation of the schizophrenic patients varied at the discretion of the psychiatrists in charge in an effort to minimize the anxiety elicited. Some patients were approached like normal volunteers (except for written consent). At the other extreme, one patient was told by the nursing staff on Tuesday morning that he was not to eat breakfast, and the participating psychiatrists then explained the procedure further.

On the morning of the procedure, subjects did not eat breakfast. As to activity, it was desirable to keep conditions at this time uniform for all subjects, but it was realized that

rigid standardization would probably be self-defeating. Subjects were simply encouraged after morning toilet to lie on their beds until further notice.

Next, if the EEG was to be recorded, an assistant applied surface scalp electrodes, either in the subject's bedroom or in some other nearby area. The subject then walked to the procedure room, where a psychiatrist usually met him and conducted a brief interview. Occasionally, schizophrenic patients were interviewed elsewhere. The subject was then asked to lie on the table.

In the next 15–30 min, the following things were done — under procaine anesthesia a 19-gage spinal needle was inserted into the right femoral artery and connected through polyethylene tubing to a heparinized blood sampling system[19] which was mounted on the table. Under procaine anesthesia a Rochester plastic needle was inserted percutaneously into a right antecubital vein. A three-way stopcock at the needle hub was connected through polyethylene tubing to the epinephrine infusion pump and to an ordinary bottle of normal saline, permitting a switch from one to the other with a minimum of dead space delay. An ECG electrode was attached to each extremity. In most studies, electrodes were attached to the soles of both feet for skin resistance recording.

VOL.
1
1962/

There followed a series of periods during which saline and epinephrine were administered alternately. Saline was always administered first, for 10, 15, or 30 min. Epinephrine was always administered for 30 min. Three schizophrenic patients and five normal subjects received two epinephrine infusions separated by 30 min of saline. In these cases, one infusion was at the rate of approximately 0·15μg of the L-base/kg/min, and the other at the rate of 0·30μg/kg/min. Three normal and two schizophrenic subjects received the low rate first; two normal subjects and one schizophrenic patient received the high rate first. One schizophrenic patient received epinephrine only at the high rate.

After these nine subjects had been studied, it was decided to shorten the procedure. By this time, it was clear that the higher rate of infusion had no special advantage, and that the original procedure was unnecessarily tedious, particularly for the more disturbed schizophrenic patients, most of whom had not yet been studied. Accordingly, the remaining sixteen subjects (eight normal and eight schizophrenic) received epinephrine 0·15μg/kg/min for 30 min, preceded and followed by saline. Recording of the EEG was also discontinued at this time.

The epinephrine used was a freshly prepared mixture in normal saline of commercial L-epinephrine bitartrate* and H^3-labeled DL-epinephrine bitartrate† in varying ratios depending on the specific activity of the radioactive material. A small amount (1 mg) of ascorbic acid was added to each 100 ml of the mixture. The infusion rate was determined by the total amount of the L-isomer in the mixture and is listed for each subject in the third paper of this series[15]. The considerable variation among individuals in the amount of D-form received was probably unimportant, since the isomer is practically inert and the two groups of subjects were made comparable in this regard.

Average and instantaneous femoral artery blood pressure were recorded continuously and simultaneously on separate channels of a Sanborn recorder by means of two strain

* Kindly supplied by Winthrop Laboratories.
† New England Nuclear Corporation.

TABLE 2. EFFECTS OF EPINEPHRINE ON BLOOD PRESSURE AND HEART RATE

		Week prior to study (average)			Initial saline period (average)			Epinephrine period (0·15 μg/kg/min)									Final saline period					
		SP (mm Hg)	DP	*** P (per min)	SP (mm Hg)	DP	** P (per min)	Early SP (Min)	Time (sec)	* Early SP (Max)	Time (sec)	** Slope of SP Rise	SP Av	DP Av	P at SP (Min)	P Av	Early SP (Min)	Time (sec)	SP Av	DP Av	P at SP (Min)	P Av
SCHIZOPHRENIC PATIENTS	S 4†	92·4	53·2	77·6	104·5	70·4	115·3	88	37	117	94	0·54	99·5	65·1	132	127·7	92	46	103·4	71·4	128	122·4
	S 1	104·8	62·8	72·0	126·2	71·3	76·7	75	41	145	113	0·97	114·0	60·1	104	110·3	79	83	110·7	64·7	108	102·1
	S 6	114·4	71·6	79·2	94·7	55·9	65·7	88	66	123	133	0·66	111·9	51·4	84	81·3	88	54	110·6	62·0	92	77·1
	S10	114·8	70·0	70·4	137·8	81·1	73·3	112	65	162	140	0·92	141·3	71·7	96	82·6	103	147	136·0	83·8	92	80·0
	S 3	114·8	75·6	77·2	99·8	71·8	79·1	85	88	108	142	0·39	100·9	69·1	104	89·3	92	28	105·3	74·7	98	89·4
	S12	110·0	78·8	72·8	117·3	72·7	80·2	88	53	123	137	0·43	103·9	59·2	110	99·2	88	30	105·6	67·2	108	94·0
	S 2	101·2	59·6	62·4	130·9	81·9	80·0	104	68	142	145	0·45	132·6	75·6	100	93·5	105	39	122·5	74·4	98	79·5
	S 7	92·8	52·7	78·8	99·0	64·3	81·6	83	63	122	111	0·71	110·4	67·6	100	91·8	105	59	108·8	71·3	98	94·4
	S11	100·4	69·6	76·0	115·7	75·7	75·8	85	62	124	135	0·59	119·1	78·0	100	83·1	92	73	103·7	71·5	106	99·3
	S 9	110·8	72·8	72·0	118·6	71·8	83·0	105	60	134	123	0·46	126·7	72·2	86	86·0	102	103	116·0	68·5	96	86·6
	S 8	102·4	67·6	71·2	111·6	78·0	76·6	95	48	126	74	0·77	112·8	70·3	100	99·4	102	26	109·7	76·9	104	86·6
	Av	105·4	66·8	73·6	114·5	72·3	80·7	92	59	130	123	0·63	115·7	67·3	102	94·9	95	63	112·0	71·5	103	91·6
	± S.D.	8·3	8·7	4·9	12·3	7·4	12·4	11	14	15	23	0·19	13·3	7·8	13	14·0	9	37	9·8	6·0	10	13·1
NORMAL SUBJECTS	N14	102·0	69·2	62·8	98·8	58·5	57·9	68	—	109	—	0·71	96·4	50·0	94	83·8	—	—	—	—	—	—
	N 3	101·6	63·6	66·8	115·2	66·5	68·9	94	44	140	90	1·11	104·3	57·0	98	97·5	85	65	109·5	66·4	98	84·6
	N 6	98·4	61·0	76·4	120·6	79·7	75·8	90	52	158	73	2·33	119·8	69·6	94	98·7	98	82	108·1	72·5	102	105·5
	N 1	98·8	63·6	64·8	107·1	68·5	83·0	105	58	152	117	0·76	139·2	76·3	74	79·6	120	93	125·5	74·8	84	68·0
	N 7	105·6	66·0	61·2	108·1	59·6	70·7	75	43	124	90	1·00	111·2	53·5	86	89·1	95	31	123·4	70·0	88	93·2
	N 5	98·8	63·2	65·6	126·6	85·4	80·7	105	50	160	105	1·00	127·4	80·0	104	114·9	108	21	116·6	80·4	124	102·1
	N 4	106·0	63·2	54·0	128·6	74·6	55·0	101	63	171	123	1·22	142·5	71·1	102	74·9	114	102	117·7	69·0	74	73·0
	N 2	112·0	61·6	70·4	129·9	81·3	72·0	110	52	149	113	0·64	115·3	70·6	108	91·2	100	34	112·6	76·8	94	85·8
	N 8	99·2	64·0	63·6	122·9	75·2	60·8	92	58	134	108	0·86	122·4	69·2	92	93·4	107	23	127·0	76·3	104	77·4
	N 9	107·2	62·0	61·2	128·3	67·9	53·6	92	57	177	110	1·79	148·2	70·2	104	75·3	104	71	125·4	72·4	84	75·5
	N11	105·6	57·2	62·8	112·5	77·4	74·2	78	44	123	156	0·33	109·6	73·7	128	112·9	80	23	116·2	85·0	120	98·2
	N12	114·4	74·2	57·6	137·7	81·7	68·8	95	59	153	115	1·02	122·6	78·2	104	108·2	94	100	117·6	78·2	104	85·1
	N10	100·4	69·2	60·0	106·2	69·1	79·2	76	62	125	98	1·47	104·2	84·0	110	89·4	85	92	105·7	71·2	92	85·5
	Av	103·9	64·1	63·7	118·7	72·7	69·3	91	54	144	108	1·10	120·2	69·5	100	93·0	99	61	117·1	74·4	97	86·2
	± S.D.	5·2	4·3	5·9	11·6	8·5	9·8	13	7	20	21	0·52	15·8	10·2	13	13·2	12	33	7·2	5·3	15	11·8

Explanation of Symbols: SP = Systolic Blood Pressure; DP = Diastolic Blood Pressure; P = Pulse rate. Significance levels of differences between groups (*t* test): * = 0·1; ** = 0·05; *** = 0·01. Subjects S1, N3 and N1 had previously received a higher dose of epinephrine (see text). Schizophrenic subject, S5, received only the high dose, and is omitted. Absolute times for subject N14 were unreliable, but SP slope was computed from relative times. † Studies were performed alternately on normal and schizophrenic subjects. (Subjects in each group are listed in the order in which they were studied.)

gages. Samples of arterial blood were withdrawn at predetermined intervals. For glucose determination, 5 ml samples were obtained in heparinized syringes 1 min before epinephrine, at minutes 5, 13, 21 and 29 during epinephrine, and 5, 15, 30 and, sometimes, 60 min after epinephrine. The total amount of blood withdrawn during each study was 200 ml or slightly less. In the case of three schizophrenic and four normal subjects, 5-minute electroencephalogram samples were obtained during saline and epinephrine periods with a standard Grass instrument, while the subjects' eyes were closed.

It was decided that efforts to conduct a truly "double blind" study would be fruitless. Observers could have obtained many unavoidable cues as to the nature of the substance being administered. It was possible, however, to keep the subjects from identifying the moments when the transition from one substance to another occurred. The manipulations involved in such a transition consisted simply of engaging or disengaging the gears of the infusion pump, and turning the stopcock. Both procedures were effectively masked by sham manipulations. Once an actual transition had been made, subjects usually quickly reported new sensations.

VOL.
1
1962/

The method of analyzing the blood pressure records was as follows — the first 15 sec of each minute were analyzed. Blood pressure varied by as much as 35 mm Hg within 15 seconds, particularly during the hyperpnea caused by epinephrine, so the value tabulated was a visual estimate of the 15-second average. Pulse waves were counted and multiplied by four to obtain heart rate. Pressure maxima and minima during and after epinephrine were tabulated as instantaneous values. Pulse rates at the times of early systolic pressure minima during and after epinephrine were determined as indices of immediate effect on pulse rate.

Estimates of the timing of inflection points on the systolic blood pressure curve during and after epinephrine were made. The early minimum during epinephrine could always be identified with confidence. The subsequent rise usually ended in a well-defined maximum peak, but occasionally it was necessary to make a rougher estimate of the time at which the rising pressure reached a plateau. The rate of pressure rise in the time interval thus defined was computed. The time at which systolic pressure reached a minimum after stopping epinephrine was tabulated, with the intention of correlating this time with blood epinephrine disappearance rate. However, pressure fall after epinephrine was frequently small relative to respiratory pressure variations, and best-fitting curves could not be drawn with any confidence. The time intervals selected are therefore at best only a very rough index of the rate at which the effect of epinephrine on blood pressure disappeared.

Average pressures and pulse rate in the various periods were computed from the minute-to-minute values. In the case of the initial saline period, all minute-to-minute values were averaged. In the case of subsequent periods, values for the first 5 min of each period were omitted from the computation to achieve a more valid estimate of the steady state. Average morning supine pulse rate and blood pressure (auscultatory) for the week preceding the procedure were computed from the measurements made routinely by members of the nursing staff.

Blood samples for glucose determination were placed in ice as soon as they had been drawn, and were analyzed within three hours by a modification of the glucose oxidase method[20].

The bilateral, bipolar EEG recordings between central and occipital areas were analyzed visually to determine alpha frequency, alpha percentage, and occurrence of abnormalities.

RESULTS

Circulatory variables

The data appear in Table 2. Semischematic average curves of systolic blood pressure and pulse rate for the two groups are presented in Figs. 1 and 2.

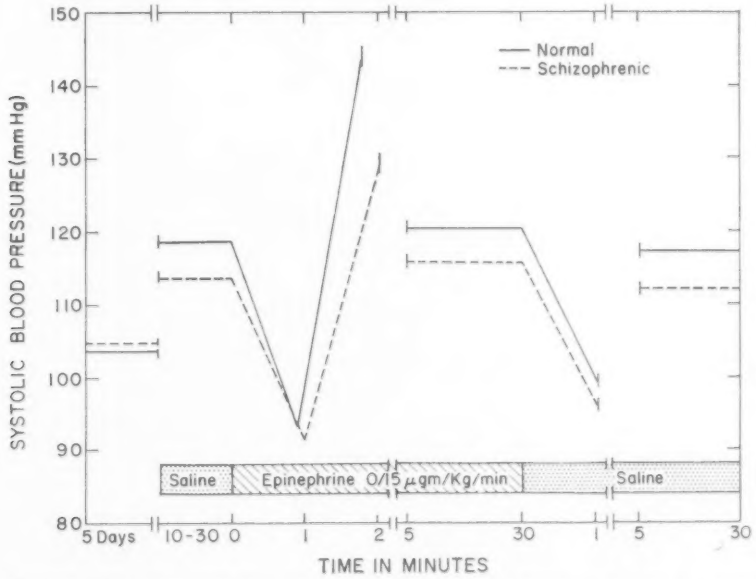

FIG. 1. Semischematic representation of average systolic blood pressure response to epinephrine.

During the week preceding the procedure, blood pressure was virtually identical in the two groups. The schizophrenic patients had higher pulse rates. On the day of the procedure, during the first saline infusion, pressure and pulse rate were relatively higher in both groups, but the groups did not differ significantly with respect to the magnitude of this increase.

The responses of the two groups to epinephrine were qualitatively similar, but with significant quantitative differences. Schizophrenic patients tended to have a smaller initial decrease in systolic blood pressure. The subsequent rise in systolic pressure was smaller, relative to the preceding minimum (mean for schizophrenic patients + 38·0 ± 12·7, normal + 53·0 ± 15·7, $p<0.05$) but was not significantly smaller relative to the saline value. The rate of systolic pressure change from minimum to maximum was the circulatory variable which distinguished most clearly between the two groups, being on the average 43 per cent less in schizophrenic patients. Only one normal subject was below the schizophrenic average and median, and no schizophrenic patient was above the normal average or median.

If one corrects for difference between groups of 5 mm Hg in control systolic pressure,

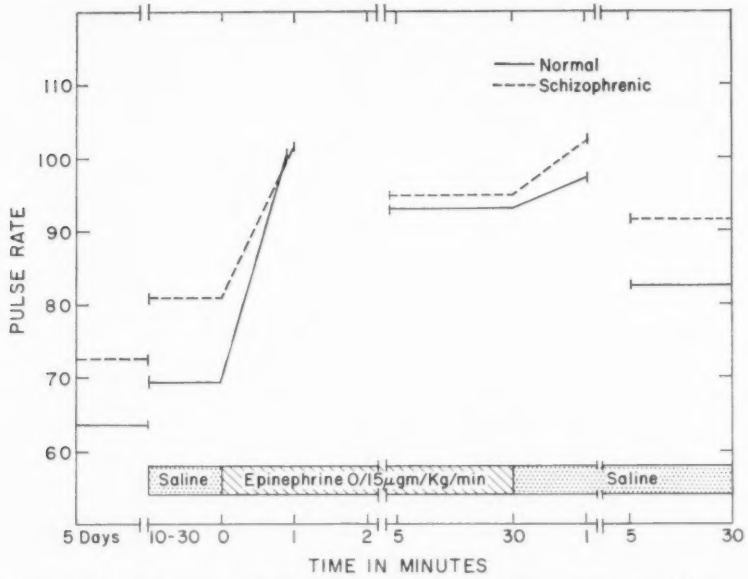

FIG. 2. Semischematic representation of average heart rate response to epinephrine.

average values after the first 5 min of epinephrine to the end of the study are virtually identical.

It should be emphasized that Fig. 1 exaggerates the pressure fluctuations which occurred soon after epinephrine was started or stopped. The high and low points each represent the average of eleven or thirteen instantaneous extremes, whereas each horizontal segment represents the average of 3000 to 6000 pulse waves, occurring in all phases of respiration.

The initial increase in pulse rate during epinephrine administration tended to be less in schizophrenic patients than in normals, but because of the unusually large variance in the normal group, the difference between groups falls short of significance. However, when pulse rate during the initial saline period is compared to average pulse rate in the last 25 min of epinephrine, pulse rate increase is significantly less in the schizophrenic group (mean for schizophrenic patients $+14{\cdot}2 \pm 8{\cdot}5$, normal mean $+23{\cdot}9 \pm 11{\cdot}2$, $p<0{\cdot}05$). Immediate pulse rate increase after stopping epinephrine is similar in both groups. Pulse rate during the final saline period is higher than the control rate in both groups, but the two groups do not differ significantly with respect to change in rate relative to either control or epinephrine periods.

Table 2 and Figs. 1 and 2 include the three subjects who received epinephrine at a rate of $0{\cdot}30\mu$g/kg/min before they received the usual lower dose. Their values during the initial saline period and during the later low-dose epinephrine infusion are included in the averages. These subjects do not affect the averages in any consistent manner, and if they are omitted from the calculations, the results and conclusions are similar, except that difference between the two groups in initial pulse rate increase during epinephrine becomes highly significant.

TABLE 3. ARTERIAL BLOOD GLUCOSE RESPONSE TO EPINEPHRINE

		Blood glucose (mg %)		Initial** slope of rise (mg%/min)	** Area (mg%×min)
		Admission (venous)	Before epi.		
SCHIZOPHRENIC PATIENTS	S 5†	72	97	2·9	1107
	S 4	84	91	1·9	553
	S 1†	66	87	2·5	1009
	S 6	71	86	3·4	1188
	S10	90	92	3·0	974
	S 3	81	87	3·6	1328
	S12	83	86	2·9	1068
	S 2	76	82	2·0	735
	S 7	79	92	2·5	922
	S11	77	85	2·3	937
	S 9	80	93	3·1	1187
	S 8	87	77	2·9	1168
	Average ± S.D.	78·8 6·9	87·9 5·4	2·75 0·52	1014·7 213·3
NORMAL SUBJECTS	N 3†	62	81	3·0	1228
	N 6	—	84	3·8	1345
	N 1†	84	83	4·0	1549
	N 7	80	90	3·5	1208
	N 5	68	84	3·1	1192
	N 4	67	83	3·5	1234
	N 2	75	81	3·0	1042
	N 8	76	83	2·0	827
	N 9	64	78	3·0	1218
	N11	—	91	4·3	1601
	N12	86	85	3·8	1381
	N10	100	96	3·4	1233
	Average ± S.D.	76·2 11·7	84·9 5·0	3·37 0·59	1254·8 205·6

† Data on these subjects represent response to 0·30μ/kg/min of epinephrine. Subject N14 is omitted from the table because data comparable to other subjects were not obtained. (Significance levels as in Table 2.)

Blood glucose

Values for blood glucose appear in Table 3 and Fig. 3. Both groups had similar fasting venous concentrations at the time of admission to the hospital. Arterial blood glucose in the initial saline period of the study was approximately 9 mg % higher in both groups. As peripheral arteriovenous glucose difference is small in the fasting state, the higher values

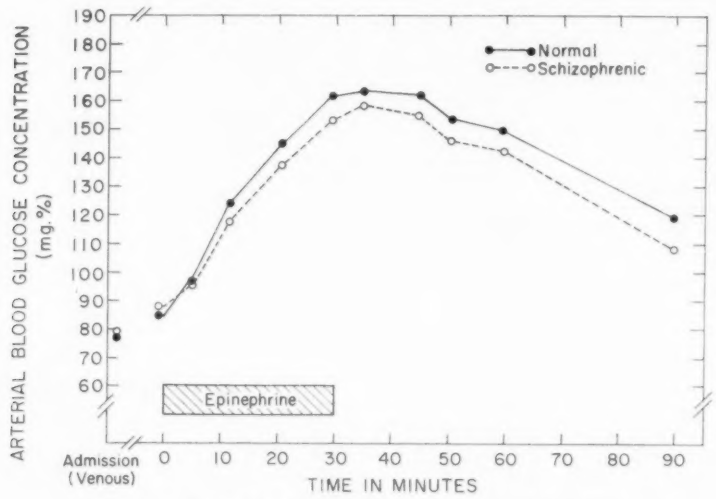

FIG. 3. Average arterial blood glucose response to epinephrine.

at the time of the study are probably partly a result of increased sympathetic nervous activity, similar to the corresponding elevations of pulse and pressure.

During epinephrine, in the schizophrenic group, blood glucose increased less rapidly, and the area under the glucose curve was smaller (expressed as total mg % minutes in 29 min). After epinephrine was discontinued, the two groups had similar disappearance curves.

EEG

Abnormalities (slow waves, asymmetries, or spikes) did not occur at any time in either group of subjects. In both groups of subjects, epinephrine had no effect on the frequency of the alpha activity. Alpha rhythm expressed as percentage of total time was more variable in both groups, but failed to show any consistent trends as a result of epinephrine administration.

The absence of any marked effect of epinephrine on the EEG under these experimental conditions is not surprising. GIBBS and MALTBY[21] have shown that intravenous epinephrine causes increases in alpha frequency of the order of $1\frac{1}{2}$ c/s in subjects who are relaxed at the time the drug is administered. They noted, however, that an increase in the level of arousal of the subject by environmental stimuli caused an equally marked increase in alpha frequency. One may assume that the level of arousal of subjects in the present experiment was sufficiently marked as to preclude the detection of the effects of epinephrine.

In summary, the effects of the infusion of epinephrine on blood pressure, pulse rate, and blood glucose were smaller and tended to occur less rapidly in the schizophrenic patients than in the normal subjects. By contrast, the effects of stopping epinephrine were similar in the two groups. None of the many variables measured distinguished without overlap between groups.

VOL. 1 1962

DISCUSSION

With respect to heart rate, arterial blood pressure, and blood glucose concentration, the responsiveness of schizophrenic patients as a group to the intravenous administration of epinephrine was found to be significantly diminished in comparison with a normal group. These results confirm with somewhat different techniques several of the findings of previous authors[1–6].

A number of possibilities present themselves as explanations for these findings. If circulating epinephrine were destroyed more rapidly in schizophrenic patients, as had been suggested at one time on the basis of *in vitro* studies[22], then equivalent infusion rates in normals and in schizophrenic patients would nevertheless result in a lower blood concentration in the latter group. In the third paper of this series[15] are presented the arterial blood concentrations of infused epinephrine at various times during the procedure. The blood levels reached, as well as the calculated rates of decay, were not significantly different in the two groups.

OL.
1
62/63

At least three general factors irrelevant to the schizophrenia or, at best, incidental to it were differently represented in the two groups studied. They are age, use of tobacco or coffee, and physical fitness or the frequency of indulgence in strenuous physical exercise. Cardiovascular responsiveness could well be correlated with age and, in fact, a coefficient of correlation of −0·48 was found within the schizophrenic group between age and rate of systolic pressure rise after epinephrine. On the other hand, FREEMAN and CARMICHAEL[2], who also reported a diminished systolic pressure response to the infusion of epinephrine in schizophrenic patients, found a correlation with age for that variable of only −0·18. The data of BACKLIN[23] also indicate that the effect of age is small. Chronic cigarette smoking and, perhaps, the habitual use of coffee, both of which were found more commonly in the schizophrenic group, could conceivably, by virtue of their repetitive autonomic stimulation, produce an adaptation to sympathomimetic effects of epinephrine, although correlations within the two groups do not support this possibility. Habitual strenuous exercise, more frequent in the normal group, is known to be associated with metabolic and cardiovascular adjustments designated by the term "physical fitness", and which might have been elicited by the circulatory and blood glucose response to epinephrine, although, here again, no support is found within the data.

Although among these possibilities, age alone was found to be suggestively correlated with any of the responses in question, only a further study better controlled for these variables could properly evaluate their significance.

It is unlikely that any one of such general factors accounts for all the differences in physiological response observed between groups. In general, intra-individual correlation coefficients among indices of pulse rate, blood pressure, and blood sugar responses are low, and do not approach statistical significance.

If a diminished responsiveness to epinephrine were shown to be a characteristic and relevant feature of certain of the schizophrenic illnesses, considerably more information would be necessary before it would be possible to suggest whether this attribute were secondary to the psychological stress and anxieties which appear to be a prominent feature of the disorder, or to what extent it was related to the etiology or pathogenesis of the disorder

itself. Information pertinent to this question may emerge from a more systematic and comprehensive attempt to disclose significant intra-individual correlations among the many variables considered in this study. That will be the subject of a separate report.

SUMMARY

(1) Observations were made on heart rate, intra-arterial blood pressure, blood glucose concentration and the electroencephalogram in alternate studies on twelve chronic, schizophrenic males and thirteen normal male volunteers, before, during and following the intravenous infusion of L-epinephrine bitartrate.

(2) The responses of the two groups to epinephrine were qualitatively similar but with significant quantitative differences.

(3) The rate of systolic pressure change from minimum to maximum during the first three minutes of epinephrine infusion was the circulatory variable which distinguished most clearly between the two groups, being on the average 43 per cent less in schizophrenic patients.

(4) The pulse rate increase during epinephrine infusion was significantly less in the schizophrenic group than in the normal volunteers.

(5) In the schizophrenic group, blood glucose concentrations taken during epinephrine infusion increased less rapidly than in the normal controls and the area under the glucose curve was smaller.

VOL.
1
1962/

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OL.
1
62/63

THE PHYSIOLOGICAL AND PSYCHOLOGICAL EFFECTS OF INTRAVENOUSLY ADMINISTERED EPINEPHRINE AND ITS METABOLISM IN NORMAL AND SCHIZOPHRENIC MEN—II.

PSYCHIATRIC OBSERVATIONS

VOL.
1
1962/

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THE TWO other papers in this series deal with certain physiological and biochemical aspects of a study of the infusion of epinephrine in a group of schizophrenic patients and a group of "normal" volunteers[1,2]. The present report is concerned with the emotional and behavioral effects observed as part of the same multidisciplinary study. A later paper will deal with intercorrelations within and between biochemical, physiological and psychiatric data.

The primary goal of the study was an investigation of the possible role played by epinephrine, or some of its metabolites, in producing the symptom picture of schizophrenia. This hypothesis was developed by Smythies, Osmond and Hoffer, who suggested that during the metabolism of endogenous epinephrine by schizophrenic patients certain psychotomimetic substances were produced[3,4].

In addition to this specific hypothesis, the widely accepted relationship between stress and schizophrenia, and between stress and epinephrine secretion, was of interest. A variety of differences between schizophrenic patients and non-schizophrenic subjects in response to epinephrine have been reported: some psychological[5] and some organic[6,7]. However, the significance of these differences — most of them separately made in a variety of populations — has not been clear.

In view of recent progress in clarifying the metabolism of epinephrine[8,9] and the availability of isotopic labelling techniques, it was thought to be of interest to compare the metabolism and the simultaneous effects — psychological, biochemical and physiological — of an intravenous infusion of isotopically labelled epinephrine in a group of schizophrenic patients and a group of "normal control" volunteers.

METHODOLOGY

A. Subject population

Twenty-four male subjects were studied, twelve of whom were chronic schizophrenic patients and twelve "normal control" volunteers.*

TABLE 1. EPINEPHRINE STUDY SUBJECTS

		Age at time of study (year)	Family history status*	Length of stay at time of study (month)	Weight change (Kg)**	Years of schooling	Psychiatric diagnosis (March, 1959) *** Schizophrenic reaction, Subtype
A. SCHIZOPHRENIC PATIENTS	S-1	35	1	12	+0·7	16	Paranoid
	S-2	31	1	17	+0·6	11·5	Paranoid
	S-3	34	2	15	+0·4	12	Simple and hebephrenic features
	S-4	38	2	12	0	10	Paranoid
	S-5	38	1	12	+1·3	10	Catatonic, with paranoid features
	S-6	30	3	13	+0·4	11	Catatonic
	S-7	37	3	17	−0·6	10	Mixed catatonic and hebephrenic features
	S-8	27	2	19	−1·8	9	Hebephrenic
	S-9	35	1	12	−1·8	10	Undifferentiated, with paranoid and catatonic features
	S-10	28	1	8	−2·2	11	Undifferentiated
	S-11	29	3	11	−2·8	6	Undifferentiated
	S-12	41	1	3·5	+1·1	13	Catatonic, with hebephrenic features
	Mean	33·5	—	13	−0·09	10·2	
	S.D.	4·8	—	4	1·4	2·4	
B. "NORMAL CONTROL" VOLUNTEERS	N-1	19	1	0·6	−0·9	12	Normal
	N-2	22	1	7	+3·7	14·5	Character disorder
	N-3	20	1	3	−0·3	14·5	Normal
	N-4	23	1	6	+0·1	12	Normal
	N-5	18	1	2	+0·1	12·5	Normal
	N-6	21	1	1	+2·8	13	Normal
	N-7	19	1	2	−0·9	12	Normal
	N-8	19	1	2·5	−0·5	13	Normal
	N-9	21	1	2	+0·7	12	Normal
	N-10	20	1	1·5	+0·2	12·5	Normal
	N-11	18	1	0·5	−1·8	12	Normal
	N-12	21	1	1	+0·15	14	Adjustment reaction of young adulthood
	Mean	20·1	—	3	+0·05	12·9	
	S.D.	1·5	—	2	1·57	0·9	
		$p = < 0.001$	—	$p = < 0.005$	n.s.	$p = < 0.001$	

* Family history status — 1 = Negative; 2 = Positive-recessive; 3 = Positive-dominant
** Weight change (Kg) within month prior to study.
*** Diagnosis for "normal control" volunteers made at the time of admission.

*The first paper in this series[1] includes physiological results from the first and pilot study in which psychiatric observations during the infusion were not made.

The *schizophrenic patients* were a carefully selected group, screened from 3,480 state hospital patients with a diagnosis of chronic schizophrenia. The goal of this screening process was to provide a representative patient group which included all of the common subtypes of chronic schizophrenia, and which met specified criteria as to age, family history, length of illness and a number of additional factors. The detailed criteria used in selecting this group, their rationale and application, have previously been reported[10].

The "*normal control*" *volunteers* were drawn from a resident group of young people who volunteered to spend protracted periods of time, varying from several months to two years, on the wards of the Clinical Center of the National Institutes of Health to participate in a variety of research studies. A previous paper described the motivations, incidence of psychopathology and other psychological characteristics of an earlier similar group of "normal control" volunteers[11]. The bulk of these volunteers are drawn from several small pacifist church sects; for most of the males their stay here is part of the time they spend as conscientious objectors. All "normal control" volunteers who had any suggestion of schizophrenia in their family history, or who, themselves, gave any indication of ambulatory, or borderline, psychosis, were eliminated from this study. Of the twelve "normal control" volunteers selected to participate in the study, two showed clinically diagnosable psychopathology.

Table 1A describes the twelve schizophrenic patients with respect to diagnosis, age, family history, years of schooling, length of stay at the National Institute of Mental Health

TABLE 2. MMPI PROFILES — 12 EPINEPHRINE STUDY MALE "NORMAL CONTROL" VOLUNTEERS AND STANDARDIZED SCORES FOR MALES

Subj.	L	F	K	Hs+ (·5k)	D	Hy	Pd+ (·4k)	Mf	Pa	Pt+ (1k)	Sc+ (1k)	Ma+ (·2k)	Si
N- 1	6	1	22	12	13	26	21	22	9	31	28	26	13
N- 2	9	1	22	14	17	24	22	41	10	26	25	23	16
N- 3	9	3	21	16	18	25	22	28	10	30	32	22	16
N- 4	9	4	19	10	17	20	25	32	7	30	26	19	32
N- 5	7	1	25	13	22	20	26	22	8	31	28	19	24
N- 6	13	5	11	8	16	14	10	25	10	29	26	14	37
N- 7	5	5	23	15	19	22	25	19	10	31	28	15	34
N- 8	12	2	16	10	8	20	18	24	10	35	33	24	21
N- 9	9	7	8	9	21	14	24	33	7	22	19	12	38
N-10	10	3	26	22	18	30	24	29	12	33	31	13	21
N-11	11	4	19	12	16	23	24	35	11	33	28	22	18
N-12	14	11	12	8	17	19	32	31	11	25	31	34	34
NIH N.C.V. MALES*	0–10	0–12	10–25	7–18	8–25	13–28	14–30	16–38	4–15	18–37	18–36	12–28	11–40
NAT'L STD MALES**	0–10	0–12	2–23	3–19	9–25	9–27	11–28	10–30	1–15	13–33	12–32	9–25	6–43

* Normal range (Mean ± 2 standard deviations) for 60 male, "normal control" volunteers admitted to NIMH during period 1954–59.
** Normal range as above.

VOL. 1 1962

PSYCHOL.
1
92/63

TABLE 3. PSYCHIATRIC EVALUATION OF 12 SCHIZOPHRENIC PATIENTS (APRIL, 1960)

	I. General appearance and manner						II. Affect and mood				III. Content of thought and thought processes						Totals		
Subjects	Motor activity	Facial Expression	Attitude to examiner	Appearance and dress	Destructive behavior	Speech	Amount of affect	Inappropriateness of affect	Mood	Anxiety	Thinking disorder	Paranoid trends	Hallucinations	Insight	Sensorium	Judgment and abstracting ability	(ΣPositive)	(ΣNegative)	(Total score)
S-1	+1	−1	+2	0	−2	+2	+4	0	−2	+2	+3	+4	0	+1	0	0	+19	− 5	24
S-2	0	+2	−1	0	+3	+1	+3	+4	+3	+1	+6	+8	+7	+4	0	+3	+44	− 1	45
S-3	−2	−3	−2	−3	−2	−1	−4	+4	−3	+2	+6	+7	+6	+4	0	+3	+32	−20	52
S-4	−1	−2	−1	0	+3	−2	−6	+4	−3	−2	+7	+8	+6	+3	0	+2	+33	−17	50
S-5	+1	−2	−1	0	+2	−2	−4	+4	−2	+2	+5	+6	+6	+4	0	+3	+33	−11	44
S-6	+2	−3	−2	+1	+1	−4	−6	+4	+3	−2	+4	+6	+6	+3	0	+3	+33	−17	50
S-7	−5	−5	−5	−2	−1	−7	−5	+6	−3	+2	+9	+6	+4	+5	+4	+7	+43	−33	76
S-8	+5	+6	−3	−2	−1	−3	−6	+6	+4	+3	+7	+6	+4	+4	+7	+7	+59	−15	74
S-9	+1	−3	−3	−1	−2	+1	−4	+6	−3	+4	+4	+8	+4	+5	+4	+4	+41	−16	57
S-10	+1	−2	−1	−1	+2	−2	−4	+2	−2	−1	+4	+5	+6	+1	0	+3	+24	−13	37
S-11	−5	−6	−6	−2	−4	−7	−6	+6	−3	+3	+7	+6	+6	+4	+5	+6	+49	−39	88
S-12	−4	−5	−4	+1	−1	−7	−7	+6	−3	+4	+6	+6	+4	+5	+2	+6	+40	−31	71

Scoring Key[13]: 1. *Motor activity:* −9, Catatonic Stupor; −7, Waxy flexibility, may obey commands; −1, Underactive—sits, lies quietly, will speak; 0, Average motor activity, relaxed; +1, Restless, tense, random movements, but sits for interview; +4, Agitated, paces room, but can be interviewed; +8, Panicky, constant motion, can't be interviewed. 2. *Facial expression:* −7, Masklike; −5, Morosely depressed; −3, Moderately depressed, miserable; −1, Anxious, tense; 0, Average; +1, Self-satisfied; +5, Inappropriate smiling and laughing; +8, Ecstatic. 3. *Attitude towards examiner:* −9, Completely oblivious of examiner; −7, Avoids examiner consistently; −4, Silent through interview though capable of talking; −3, Uncooperative, resistant, negativistic; −1, Tolerates interview; guarded; 0, Welcomes, appropriately open, comfortable; +1, Too friendly, too eager to cooperate, seductive; +2, Effusive, over-eager to tell story, fights termination; +6, Repeatedly clings physically to examiner. 4. *Appearance and dress:* −9, Smearing self and surroundings; −5, Tearing off clothes; −3, Odorous, torn, filthy clothes; −1, Poor personal hygiene, poorly dressed; 0, Normal hygiene and dress; +1, More than average attention to dress and toilet; +2, Compulsive cleanliness and dress; +7, Bizarre attention to details of dress, toilet. 5. *Destructive behavior:* −8, Attempts suicide, self-mutilation; −4, Threatens suicide, self-mutilation; −2, Extremely self-depreciatory; 0, Normal — expresses hostility appropriately, under control; +1, Hostile to examiner; +3, Threatens assault or destruction of property; +7, Actual assaultiveness to examiner, staff, destroys property. 6. *Speech:* −9, Mutism; −6, Blocking and prolonged silence; −1, Under-talkative; 0, Normal amount of speech; +1, Overtalkative; +3, Voluble, can restrain himself with difficulty; +7, Logorrhea, flight of ideas. 7. *Amount of affect:* −9, Completely flat affect; −6, Blunted affect; −4, Bland affect; −1, Reserved, decreased affect displayed; 0, Normal; +1, Demonstrative, affect displayed more freely than usual; +3, Labile, outbursts are controllable; +7, Explosive, uncontrollable displays of affect. 8. *Inappropriateness of affect:* 0, Appropriate affect; +2, Questionably inappropriate affect; +6, Definitely inappropriate affect; +9, Continuously inappropriate affect. 9. *Mood:* −7, Profoundly depressed; −3, Despondent, gloomy; −1, Pessimistic; 0, Average, ordinary mood; +1, Optimistic; +4, Euphoric; +8, Manic exaltation. 10. *Anxiety:* −2, Phlegmatic, no show of anxiety where anxiety would be expected; 0, Average; +1, Sensitive, easily made anxious, tense; +3, Moderately anxious with some somatic symptoms – shortness of breath, palpitations, moist palms, tremor; +7, Panic, feeling of impending doom. 11. *Thinking disorder:* 0, No evidence of thought disorder; +1, Circumstantiality; +4, Some loosening of associations; +7, Marked thought disorder, autistic thinking; +9, Fragmented thinking, word salad, neologisms. 12. *Paranoid trends:* 0, No suspiciousness, no delusional material; +2, Suspiciousness with delusions; +3, Unfixed delusions; +6, Unsystematized fixed delusions; +8, Well systematized fixed delusions. 13. *Hallucinations:* 0, No hallucinations; +3, Questionable whether patient is hallucinating; +5, Present but patient questions reality of hallucinations; +9, Hallucinations present most of the time, patient preoccupied with them and not questioning the reality of them. 14. *Insight:* 0, Some true emotional insight; +1, Intellectual insight only; +3, Admits problem, but is not concerned; +5, Denies existence of any problem. 15. *Sensorium:* 0, Fully oriented; +2, Minimal disorientation; +4, Moderate disorientation; +7, Severe disorientation. 16. *Judgment and abstracting ability:* 0, Accurate, appropriate and abstract responses; +2, Mild impairment; +4, Moderate impairment; +7, Autistic, bizarre responses.

prior to study and weight change during the month prior to study. Table 1B summarizes the same data for the twelve "normal control" volunteers. Personality portraits of the individual "normal control" volunteers are summarized in Table 2, which gives each "normal control" volunteer's MMPI profile[12], and the national standard and NIH normal ranges, for comparison.

The characteristic clinical state of each patient is summarized by mental status ratings, presented in Table 3. Ward behavior during the two weeks preceding each subject's study

TABLE 4. WARD BEHAVIOR RATINGS

		Exposure	Eating	Participation	Compliance–resistance	Interest	Coherence	Verbal	Relevance	Initiates contact	Activity	Anger towards others	Total score	Mean score
A. SCHIZOPHRENIC PATIENTS	S-1	1·0	1·0	1·3	2·7	1·3	1·2	3·7	1·8	0·8	2·0	2·1	18·4	1·7
	S-2	1·3	2·0	2·3	2·3	1·3	3·0	2·3	3·0	1·3	2·0	2·7	23·5	2·2
	S-3	1·2	1·1	3·0	2·7	2·0	1·9	2·1	2·4	2·0	2·7	1·7	22·8	2·1
	S-4	1·7	1·0	1·0	1·0	1·8	1·0	2·0	1·0	2·0	1·0	1·5	15·0	1·4
	S-5	1·1	1·0	1·8	1·5	1·5	1·3	1·5	1·3	1·5	1·5	1·5	15·5	1·4
	S-6	1·4	1·0	1·8	1·4	1·6	2·0	1·6	2·2	1·8	1·6	2·2	18·6	1·7
	S-7	1·5	1·5	2·3	2·0	3·0	u/l	4·0	u/l	2·8	2·8	1·5	21·4	2·4
	S-8	1·4	1·0	2·0	1·4	2·2	1·6	2·4	1·8	2·0	1·8	1·0	18·6	1·7
	S-9	1·2	1·7	2·9	3·9	2·8	1·7	2·2	2·2	1·3	2·1	2·3	24·3	2·2
	S-10	1·7	2·2	1·7	1·0	1·3	1·0	1·3	1·2	1·3	1·2	2·0	15·4	1·4
	S-11	2·0	1·9	2·4	2·2	2·6	2·5	2·1	2·5	3·1	2·6	2·8	26·7	2·4
	S-12	1·6	1·3	2·2	1·3	2·8	1·0	4·0	1·2	3·5	2·8	1·5	23·2	2·1
												Mean	20·3	1·9
B. "NORMAL CONTROL" VOLUNTEERS	N-1	1·0	1·0	1·0	1·0	1·0	1·0	1·0	1·0	1·0	1·0	1·0	11·0	1·0
	N-2	1·0	1·0	1·0	1·0	1·0	1·0	1·0	1·0	1·0	1·0	1·0	11·0	1·0
	N-3	1·0	1·0	1·0	1·0	1·0	1·0	1·5	1·0	1·0	1·0	1·0	11·5	1·1
	N-4	1·0	1·0	1·0	1·0	1·0	1·0	1·0	1·0	1·0	1·0	1·0	11·0	1·0
	N-5	1·0	1·0	1·0	1·0	1·0	1·0	1·0	1·0	1·0	1·0	1·0	11·0	1·0
	N-6	1·0	1·0	1·2	1·0	1·4	1·0	1·0	1·0	1·0	1·2	1·0	11·8	1·1
	N-7	1·0	1·0	1·0	1·0	2·0	1·0	1·0	1·0	1·0	1·0	1·0	12·0	1·1
	N-8	1·0	1·0	1·2	1·0	1·2	1·0	1·0	1·0	1·0	1·0	1·2	11·6	1·1
	N-9	1·0	1·0	1·0	1·0	1·4	1·0	1·0	1·0	1·0	1·2	1·0	11·6	1·1
	N-10	1·2	1·0	1·6	1·0	1·6	1·0	1·6	1·0	1·8	1·0	1·0	13·8	1·3
	N-11	1·0	1·0	1·0	1·0	1·0	1·0	1·0	1·0	1·0	1·0	1·0	11·0	1·0
	N-12	1·0	1·3	1·0	1·0	1·0	1·0	1·0	1·0	1·0	1·0	1·0	11·3	1·0
												Mean	11·6	1·1

$p < 0{\cdot}001$

Arithmetic mean of weekly ratings made by 2–12 nurse raters of subject during two weeks preceding each subject's study. Ratings are part of routine weekly evaluation. Items rated were selected from a 26-item nurse-rated ward behavior schedule developed for description and quantification of manifest ward behavior of subjects residing in NIMH research wards who range from "normal control" volunteers to disturbed chronic schizophrenic patients. This schedule is part of a continuing study of the process of observing and quantifying behavior of experimental subjects. Items employed are those presently considered to have the greatest reliability and validity. Full scores distinguish over and under activity on bimodal items. Scores range from 1: Normal behavior to 4: Maximal psychotic pathology, employing precise descriptions for each scoring level[14].

VOL. 1 1962/

is summarized in Table 4. In both these cases, quantified evaluation scales, developed in this laboratory, have been used [13, 14]. The mental status ratings were done in April, 1960, when the scale became available for use. Studies were conducted during the period, December, 1958 through August, 1959. Ward behaviour was rated each week of the study.

Living conditions for both groups were planned to be as similar as possible when dealing with a psychotic and a non-psychotic group. Each group lived on a ward of its own. These wards were physical duplicates of each other, and similarly staffed by nurses and ward attendants. They both partook of the same general hospital diet. The "normal control" ward was an open one, with the normal control volunteers coming and going frequently, and having considerable leeway in their choice of daily off-the-ward activities. Only four schizophrenic patients had grounds privileges and worked off the ward. For the schizophrenic group, as a whole, a planned program of ward and off-ward activities tended to equalize the over-all activity pattern of the two groups, but the "normal control" volunteer group remained more active. However, there was no statistically significant difference in weight change during the month prior to study, between the "normal control" volunteers and the schizophrenic patient group.

OL.
1
62/63

Both groups participated in a variety of other studies both before and after the epinephrine. They were both, therefore, familiar with the role of the experimental subject. There were, however, significant group and individual differences in this regard, as measured by length of stay at the National Institutes of Health prior to participation in this study. (Table 1). As a group, the "normal control" volunteers had been at the National Institutes of Health a significantly shorter period of time than the schizophrenic patient group.

B. Treatment

Most of the schizophrenic patients were receiving electroshock or ataractic drug therapy at the time of transfer to the National Institutes of Health. At that time all drug and electroshock therapy was discontinued and they had been without any organic therapy for an average period of one year at the time of this study. The schizophrenic patient care regimen included group therapy, an active milieu program based on a high staff–patient ratio, and a variable program of individual therapy. The "normal control" volunteers had no such program of group or individual psychotherapy. This fact, plus their shorter length of stay at the National Institutes of Health prior to study, resulted in their being less familiar with the psychiatrists participating in the study than were the schizophrenic patients.

C. Procedure

Detailed descriptions of the physiological, biochemical and recording techniques involved in this study are given in papers I and III.[1,2]

All the "normal control" subjects were told by their ward administrator—an internist—of the forthcoming procedure several days in advance. Among the schizophrenic patients, some were told days before the study, whereas others were told on the morning of the test. The approach judged likely to cause the least anxiety and allow the patient to participate optimally in the procedure was chosen.

One subject was studied each week, the procedure usually extending over an entire

morning and taking place in a procedure suite located on the schizophrenic patients' ward. After having EEG electrodes affixed, the subject was seen for a baseline pre-procedure interview by both authors. This interview usually took place in the procedure room itself, and provided the subject an opportunity to familiarize himself with the surroundings in which the procedure took place. For several of the more anxious schizophrenic patients, however, it was held in their own rooms.

The number of investigators and quantity of equipment present during the initial trial runs threatened to be disturbing. This difficulty was remedied in part by placing much of the equipment, the psychiatrist observer, and a number of the other investigators in an adjacent room where they could view the procedure through a one-way mirror, and communicate with the internist in the procedure room through microphone and a single earphone. Despite such efforts at simplification, however, the procedure remained an imposing one for the subject in terms of the quantity of apparatus and the number of individuals which he saw involved in the study. Such individuals routinely included the internist who coordinated the studies in the procedure room, the psychiatrist-interviewer, and several nurses, who were all present during most of the morning. A clinical investigator who placed the arterial needle, the laboratory chief, a neurophysiologist and a biochemist preparing and checking equipment or solutions, and several research assistants administering brief tests and handling the frequent blood samples, were usually present in the procedure room for only brief periods of time.

VOL.
1
1962/

After the pre-procedure interview each subject mounted a table fitted with a foam rubber mattress and an average of some thirty minutes was required for the insertion of a femoral arterial needle, an intravenous infusion needle in the antecubital fossa, and the connection of numerous sets of recording electrodes to all four extremities. There followed a thirty-minute saline infusion, a thirty-minute epinephrine infusion and another thirty-minute saline infusion. The subject had no external knowledge of the transition from saline to epinephrine, or the return to saline infusion. The epinephrine was infused at the rate of 0·15 gamma of the L-base/kg/min.*

D. Psychiatric observations and data

Background data. All "normal control" volunteers in the Laboratory of Clinical Science are seen shortly after their admission by one of several psychiatrists for a psychiatric evaluation. The evaluations of the "normal control" volunteers in this study were subsequently reviewed by one of the authors (S. G.). Schizophrenic patients were seen for extensive admission interviews by two psychiatrists, and after several weeks to months, were presented to staff conferences at which diagnostic consensus was obtained. Formal diagnostic re-evaluations, by staff conference consensus, have taken place yearly. Each of these patients has had continued extensive contact with the psychiatric and nursing staff and is well known to every team member.

*Studies N-1 – N-4 and S-1 – S-3 included one additional epinephrine infusion at a rate of 0·30 gamma/kg/min.; and one additional saline period. S-5 received only the higher infusion rate. Several schizophrenic patients prejudged likely to have considerable anxiety during the procedure had the length of saline infusion reduced to 10 or 15 min. Paper III[2] gives data as to the total amount of epinephrine administered to each subject.

TABLE 5. PSYCHOLOGICAL DIFFERENCES BETWEEN A SCHIZOPHRENIC AND A NORMAL CONTROL SUBJECT GROUP DURING EPINEPHRINE INFUSION STUDY

		Situational anxiety I	Overall ability to cope with experimental situation II	Involvement–communication III	Epinephrine response: overt anxiety IV	Epinephrine response: arousal–constriction V	Manifest anger VI	Procedural difficulties VII
A. SCHIZOPHRENIC PATIENTS	S-1	6	10	5	10	7	2	−
	S-2	9·5	16	18·5	22	14·5	2	−
	S-3	5	20·5	15	17	14·5	1	−
	S-4	22	16	14	23	18	4	−
	S-5	3·5	19	8	4	9	4	+
	S-6	14·5	11	20	14·5	12	3	+
	S-7	1	23	24	19·5	8	3	+
	S-8	2	23	23	19·5	11	4	−
	S-9	3·5	23	17	16	3	1	+
	S-10	16	8	12	21	20	4	−
	S-11	13	20·5	22	11	2	3	+
	S-12	11	13	21	18	14·5	4	−
B. "NORMAL CONTROL" VOLUNTEERS	N-1	9·5	18	7	12·5	—	2	+
	N-2	14·5	3·5	6	24	22	4	−
	N-3	18	3·5	2	3	23	4	−
	N-4	23·5	1	4	6	21	4	−
	N-5	23·5	2	10	1	6	4	−
	N-6	19·5	7	16	8	10	2	−
	N-7	19·5	6	10	7	14·5	4	−
	N-8	17	9	13	14·5	5	3	−
	N-9	12	14	10	9	1	4	−
	N-10	7·5	16	18·5	5	4	4	+
	N-11	7·5	12	3	12·5	19	2	+
	N-12	21	5	1	2	17	3	+
	Two-tailed Mann Whitney U	29	19	22·5	26·5	61·5	NS	NS
	P	<·02	<·002	<·02	<·02	NS(>·10)	Fisher's Exact Test	

Note 1 — Items I to V are consensus rankings of two independent psychiatrists whose initial separate rankings showed agreement statistically significant at the ·05 level (item 4) or the ·01 level (items 1, 2, 3, 5.)

Note 2 — Item VI represents a 1:4 rating and item VII a yes–no rating made by one psychiatrist (WP)

Procedure interview and observations. Two psychiatrists alternated as interviewer and observer during successive studies. Both were present in the same room with the subject during a brief, pre-procedure interview, which evaluated the subject's anticipatory anxiety, and his picture of the procedure to come. Subsequently the observer watched the entire procedure through a one-way mirror from an adjacent room.

The psychiatrist-interviewer played a double role: helping subjects cope with the anxiety generated by the experimental situation, as well as obtaining research data. The amount of

anxiety mobilized, particularly in the schizophrenic patients, was potentially disruptive to the extent of making the study impossible. The amount of help needed by different subjects varied, and thus different kinds of relationships were set up with different subjects.

During the early portion of each infusion period, the interviewer encouraged the subject to verbalize spontaneously, and describe in an unstructured fashion, his subjective sensations, with particular emphasis on any changes the subject noted. Later in each period a 33-item questionnaire, referring to each of the signs and symptoms described in the literature on epinephrine administration, was employed. (Table 6).

TABLE 6. SUBJECTIVE REPORTS OF CHANGES WITH EPINEPHRINE INFUSION

Item	*Number of responses	*% responses	Item rank
1. Afraid, or anxious (fearful, apprehensive)	9	50%	6·5
2. Nervous or upset?	11	61	4
3. Easy or hard to concentrate on my questions?	13	72	1
4. Easy or hard to talk to me?	12	67	2·5
5. Alert — much impressed by things about you? or Distracted — not very aware of surroundings?	8	44	8
6. Sleepy or wide awake?	10	56	5
7. Angry, irritable or annoyed?	2	12	20
8. Depressed or unhappy?	2	11	23
9. Restless?	5	28	15
10. Trembling or shaky?	6	35	11
11. Weaker or stronger?	9	50	6·5
12. Tired or drowsy?	5	29	13·5
13. Dizziness?	1	6	26
14. Headache?	2	12	20
15. Dryness of mouth?	6	35	11
16. Choking?	1	6	26
17. Other sensations head and neck?	1	6	26
18. Chest sensations?	2	12	20
19. Awareness of heart—Rate?	12	67	2·5
20. Awareness of heart—Force?	6	35	11
21. Tightness of chest?	3	18	16·5
22. Breathing difficulty?	3	18	16·5
23. Stomach?	1	6	26
24. Bowels?	2	12	20
25. Urine?	2	12	20
26. Extremities (tremor)?	7	41	9
27. Warm or cold?	5	29	13·5
28. Perspiration?	0	0	—
29. Hunger?	1	6	26
30. Different — you?	0	0	—
31. Different — I?	0	0	—
32. Different — room?	0	0	—
33. Strange feelings?	0	0	—

*Response indicates a change, either increase or decrease, of the function involved, or awareness of some new sensation in the body part mentioned, during epinephrine infusion. N, based on subjects sufficiently verbal and intact to respond meaningfully to questionnaire, = 18. (Items 7, 10, 12–18, 20–29, added after first two subjects studied: N = 17).

Both interviewer and observer kept separate running narrative accounts of each study, describing all observed behavioral changes and apparent causes or correlates. The verbal exchanges between psychiatrist and subject throughout the study were tape recorded.

Following each procedure, both psychiatrists made separate judgments as to the appearance or change of psychotic symptoms, and separate ratings, on a nine-point scale, of anxiety, relationship to environment, and affect. Following the completion of the entire study, both psychiatrists separately reviewed all twenty-four protocols. On the basis of this review, six aspects of subjects' behavior during the procedure were selected as items to be used in making comparisons between individual subjects; and between the two groups of subjects: schizophrenic patients and "normal control" volunteers. These six items were those isolatable attributes of procedure behavior which showed distinguishing variability from one subject to another, and also had significant relevance to the study goals. The six that emerged were — 1. Situational anxiety. 2. Overall ability to cope with experimental situation. 3. Involvement–Communication. 4. Epinephrine response: Overt anxiety. 5. Epinephrine response: Arousal–Constriction. 6. Total response to epinephrine. Their definitions will be given below, in presentation of *Results*. It was decided that comparing subjects directly one with another, by a ranking from one to twenty-four for each of these attributes, was preferable to adding an intermediate step of arbitrary rating standards. Separate rankings for each of the six items were therefore set up, based on each psychiatrist's separate review of all twenty-four protocols. Those items where the level of agreement between the two separate rankings was statistically significant were used for comparing the schizophrenic patient group with the "normal control" volunteer group. This was done by deriving a consensus ranking on each of these items for each subject (the mean of the two separate rankings), and then testing (by the two-tailed Mann–Whitney method) for a statistically significant difference between the distribution of rankings of the schizophrenic patient group and the "normal control" volunteer group.

RESULTS

1. *Psychotic symptomatology*

No behavior judged psychotic, or suggestive of a reality break, occurred in any "normal control" volunteer subject during any phase of the study. Seven of the twelve schizophrenic patients showed significant change in psychotic symptoms during the study. In two patients, psychotic symptoms became less prominent (S-10, S-5). In five patients there was an exacerbation of psychotic symptoms; three of these occurred during saline (S-3, S-4, S-8); and two during epinephrine infusion (S-1, S-11). In one of the two patients where exacerbation occurred during epinephrine infusion, such exacerbation was judged to be a characteristic response to an environmental stimulus, and unrelated to the epinephrine (S-1); in the other patient (S-11), a marked increase of psychotic withdrawal, which had begun prior to epinephrine, accelerated rapidly with epinephrine and was judged to be related to the epinephrine infusion. Two of the patients showing exacerbation during saline did so during saline prior to epinephrine infusion. (S-3, S-8). In the third, (S-4), it was not clear whether an unusual episode of inappropriate behavior, occurring during saline following epinephrine infusion, was most closely related to the epinephrine, or to more general stress

factors of the overall experimental situation. There were no delayed reactions occurring upon return to the ward. There was no disagreement between the two psychiatrists concerning judgments of psychotic symptoms.

S-11 showed a marked increase in withdrawal coincident with the beginning of the epinephrine infusion, proceeding to practically total mutism which persisted throughout the epinephrine period and the subsequent saline period, but subsequently subsided on his return to the ward. Such a mute, catatonic-like withdrawal is one of this patient's prominent symptoms. During the preliminary pre-procedure interview this patient had been more verbally responsive than usual and, despite a somewhat difficult procedure technically (with the need to repeat the insertion of the antecubital intravenous needle several times) had maintained this unusually high verbal level during the first portion of the saline infusion. Toward the end of the saline period he began to show increasing, but still mild tendencies toward withdrawal and diminution of his verbal responses. This appeared to be primarily a response to the enforced, persistent and continuous relationship, and physical closeness, between himself and the interviewing psychiatrist. Characteristically, on the ward, this patient's moves into withdrawal and mutism have occurred in response to such externally pressured intimacies. There was a marked increase in the amount of withdrawal and decrease of verbal responsiveness when epinephrine replaced the saline infusion.

S-1 showed a sudden upsurge of paranoid complaint (his most usual and characteristic symptom) during the last few minutes of his second epinephrine infusion. During his first infusion he functioned more adequately than was usual for him. His paranoid production began when he heard some whistling in the hall outside the procedure room door, and assumed correctly that another patient, with whom he was feuding, had somehow gained access to the procedure area and might be observing him through the door window. In anticipation of the procedure, S-1 characteristically had expressed great concern as to who might be observing him and whether he would be adequately dressed, or over exposed, as he lay on the procedure table. He is routinely concerned during interviews on the ward about the possibility of being overheard by other patients. His sudden increase of paranoid ideation, upon hearing the outside whistling, was interpreted as fitting into this typical pattern of response rather than as being specifically related to the epinephrine infusion.

Two schizophrenic patients showed a decrease in several of their typical symptoms during the period of epinephrine infusion. S-10, whose thought processes usually are extremely circumstantial, with some tendency to loose associations and failure to reach goal ideas, showed a sharp decrease in these characteristics during epinephrine infusion. They had been more than usually prominent during the pre-procedure interviews and saline infusion. This patient was aware of these changes and commented that, though he found it more difficult at that point to concentrate on questions and to respond, he found it easier to stay on one track and say what he meant. S-5, ordinarily quite distant, self-contained and given to bland denial of his obvious psychotic content and hallucinations, was in better contact than usual, more related and able to talk openly about his "voices." This was a situational rather than an epinephrine response, manifesting itself during his preliminary interview and saline infusion as much as during epinephrine infusion.

2. *Schizophrenic patient — "Normal control" volunteer differences*

Ratings of anxiety, relationship and affect, made at the time of each study, did not show a level of inter-rater agreement that was statistically significant. They will not, therefore, be referred to further in this report.

Of six behavior items for which the two psychiatrists separately ranked all twenty-four subjects following completion of the study, five showed inter-rater agreement that was statistically significant, and were therefore usable in comparing the response of the schizophrenic patients and the "normal control" volunteers in this experimental situation. Table 5 summarizes these findings, which are separately described below.

(a) *Situational anxiety*. All subjects were ranked with regard to the degree of overt anxiety demonstrated by them prior to the beginning of epinephrine infusion. This was seen as the baseline level against which epinephrine effects needed to be viewed. The correlation between the two sets of rankings was 0·569; (this was statistically significant at the 0·01

VOL. 1 1962/

level). Consensus ranking showed that the schizophrenic patients had a higher level of situational anxiety than did the "normal control" volunteers ($p=<0{\cdot}02$).

(b) *Epinephrine response. Overt anxiety.* All subjects were separately ranked with regard to overt anxiety shown during the period of epinephrine infusion. The correlation between the two sets of rankings was 0·451; ($p=<0{\cdot}05$). Consensus ranking showed that the schizophrenic patients manifested less anxiety during epinephrine infusion than the "normal control" volunteers ($p=<0{\cdot}02$). Two unusually articulate and communicative "normal control" volunteers spontaneously differentiated the "anxiety" they experienced during epinephrine infusion from actual life-situation anxiety. One said, " I have all these sensations and feelings we've been talking about, just like when I get tense before an exam, but I don't really feel afraid or anxious."

(c) *Epinephrine response. Arousal–Constriction.* The most variable response to the infusion of epinephrine was observed along an arousal–constriction axis. It was noted that all subjects showed a narrowing of their field of awareness, and a shift of attention from the environment to inner, body experience, with the onset of epinephrine infusion. Thereafter, certain subjects experienced more intensely, or preferentially reported, a number of changes suggestive of increased arousal: feelings of increased strength, alertness, attentiveness and being more wide awake. Other subjects experienced more strongly, or preferentially reported, changes suggesting decreased arousal (or constriction), feeling weaker, sleepy, less alert and more pre-occupied; emphasizing difficulties in concentration and communication, and showing impairment of their relationship with the interviewing psychiatrist. (On this item, subjects were ranked from most (#1) to least (#24) constriction; high numerical rankings therefore indicate subjects with high level of arousal.) Separate rankings on this continuum correlated 0·665; ($p=<0{\cdot}01$). However, consensus rankings showed no statistically significant difference between schizophrenic patients and "normal control" volunteers on this continuum.

(d) *Ability to cope with the experimental situation.* There were marked differences in the success with which different subjects were able adequately to cope with the overall experimental situation. (By adequate in this setting is meant the ability to go through the experimental situation without the development of extreme degrees of free anxiety, or unusual or inappropriate behavior.)

Certain subjects showed a rare feature of their customary behavior becoming considerably exaggerated, to a level never seen under normal circumstances. Thus, one normal control (N-1) who on the ward was usually quite pleasant, with rare, brief expressions of overt annoyance, became openly and persistently angered, "disgusted", and accusing toward the interviewer during the course of his study. A schizophrenic patient (S-4) ordinarily very scrupulous and proper in his behavior, but whose verbal content suggested sexual preoccupation, masturbated openly during the post epinephrine saline period. Other examples of behavior considered indicative of poor ability to cope with the situation were extreme degrees of anxiety, approaching or reaching panic, during preparatory phases of the study (S-7, S-8); intense withdrawal (S-3, N-12); or persistent anxiety symptoms during those periods of saline infusion usually experienced as anxiety-free and relaxed.

Correlation of rankings along this continuum was 0·706; ($p=<0{\cdot}01$). The consensus

ranking showed schizophrenic patients much less able to cope with the experimental situation than normal control volunteers ($p = <0{\cdot}002$).

(e) *Involvement-Communication.* Individual subjects showed considerable difference in the extent to which they became involved with, and verbally communicated their subjective experience to, the interviewing psychiatrist. Subjects were ranked from most (#1) to least (#24) involvement. The two separate rankings along this continuum showed a correlation of 0·640; ($p = <0{\cdot}01$). Consensus rankings showed schizophrenic patients ranking lower on this continuum than "normal control" volunteers; ($p = <0{\cdot}02$).

(f) *Total response to epinephrine.* Rankings of the intensity of the total epinephrine response showed an inter-rater agreement that was not statistically significant.

3. *Epinephrine response*

The subjective experiences and changes reported by subjects during the period of epinephrine infusion, are summarized in Table 6. This lists each of the thirty-three items of the questionnaire employed during the study, and the number and percentage of responses. A response indicates a change, either increase or decrease, of the function involved, or awareness of some new sensation in the body part mentioned, during the epinephrine infusion. Eighteen subjects (twelve "normal control" volunteers and six schizophrenics) were sufficiently verbal to give meaningful responses. ($n = 17$ for items 7, 10, 12–18, 20–29, which were added to a revised form after first two studies.) The most frequently reported subjective responses, with maximum percentage in each category were: (1) changes in difficulty of concentration and communication (#'s 3 and 4: 72%): (2) awareness of heart-beat change, particularly rate (#'s 19 and 20: 67%): (3) "anxiety" (#'s 1 and 2: 61%); (4) change in level of arousal (#'s 6, 11 and 5: 56%); (5) tremor (#'s 26 and 10: 41%); and (6) dryness of the mouth (#15: 35%). These were the six categories of subjectively experienced change reported by one-third or more of the reporting subjects. Subjective reports were not used as a basis for comparison of schizophrenic patients with "normal control" volunteers because of the considerable differences between the two groups in ability to report verbally their subjective experience.

The subjects' reports of subjective experience described above closely paralleled the effects observed by the two psychiatrists. Typically, the following sequence was observed with epinephrine infusion. Within one minute of the change from saline to epinephrine, the subject would draw a deep breath or heave a sigh, begin to pale, and develop a pre-occupied, tense look on his face. During approximately the first five minutes of this period there would be signs suggestive of an increase in arousal. The subject looked more wide awake, the interpalpebral fissures widened, speech became more forceful and rapid and there would be a facial expression indicative of increased attention. However, most attention now appeared to be shifted to internal bodily processes. The subject appeared pre-occupied, and less aware of what was going on about him, and of his surroundings. Though he might respond to questions more forcefully, it was more of an effort, and one of which he was often aware, to concentrate on questions or on anything outside of himself, or to try to communicate what he was feeling. He was usually subjectively aware that something new was happening. He tended to be pre-occupied by his awareness of a marked increase in the

VOL. 1 1962/

rate, and to a lesser extent, the forcefulness, of his heartbeat. Whatever mild discomfort of position, or needle site, may have been reported during saline infusion was now minimized. Tremor of the extremities was noted, most notably when the subject used his hands.

After approximately 5 min, and with no change in the rate of epinephrine infusion, the response described above would become attenuated. There would be an increase in the subject's ability to describe his inner experience and communicate with his environment. There would be evidence of some relaxation as manifested by changes of facial expression and tone of voice. The subject would describe some diminution in the increased force and rate of heartbeat and would be somewhat less pre-occupied by this. None of these conditions, however, would recede to the pre-epinephrine baseline, until some minutes after completion of the epinephrine infusion.

OL.
1
62/63

DISCUSSION

The results obtained in this study fail to support the hypothesis that an abnormality in the disposal of circulating epinephrine is responsible for the clinical features of schizophrenia. The hypothesis would have been supported had it been observed that the response of the schizophrenic patients to epinephrine infusion was qualitatively different from the response of the "normal control" volunteers; and if part of this response had been an increase of psychotic behavior, definitely attributable to the infused epinephrine. However, no qualitative difference was observed in the psychological response of the schizophrenic patients to the epinephrine infusion as compared to the response of the "normal control" volunteers. There was no significant exacerbation of psychotic symptoms in response to epinephrine among the schizophrenic patients, either during or following the infusion. Of the seven episodes of increased psychotic behavior noted during the procedure, six were felt to be a response to features of the experimental situation other than the epinephrine. Decreases of psychotic behavior were noted as well as increases.

Though these observations do not confirm the hypothesis, they cannot properly be interpreted as refuting it. These observations were based on an infusion of epinephrine which lasted 30 min. They do not indicate what the effects of much longer, chronically elevated levels of circulating epinephrine would be. Nothing in clinical experience with schizophrenia suggests that brief periods of stress, analogous to the thirty-minute epinephrine infusion, play an important role in causation of schizophrenic symptomatology. Rather, the type of stressful life situations which, on clinical grounds, appear relevant and which may be accompanied by high levels of endogenous epinephrine secretion, are characteristically chronic and prolonged, rather than brief.

Some questions can be raised as to whether a chronic schizophrenic population is an adequate subject group in which to study even the short range effects of epinephrine along the lines of this hypothesis. One may believe, for example, that once the schizophrenic process has become chronically established the possibility of noting further change would be limited. However, in the natural course of the disease, chronic patients can show marked exacerbations, with intensification of their psychotic symptoms. Each of our schizophrenic patients has shown such change at some point in his recent clinical history. Therefore, one may conclude that though a chronic patient group will be less likely to show change than

an acute patient group, it has enough potential for clinical variability to warrant its use in this type of study.

These observations provided a reliable quantitative measure of two aspects of the response to epinephrine. One of these — arousal-constriction — showed no difference between schizophrenic patients and normal control volunteers. The other — overt anxiety — did show a statistically significant difference between schizophrenic patients and "normal control" volunteers. The schizophrenic patients showed less overt anxiety in response to epinephrine infusion than did the volunteers. DYNES and TOD have reported a similar observation[5]. They employed single intra-muscular injections of epinephrine, in a chronic schizophrenic population so selected as to be composed of especially flat, non-reactive, cooperative patients. These investigators felt that the relative absence of overt anxiety in their schizophrenic patients, in response to epinephrine, reflected a basic qualitative difference between schizophrenic and normal individuals, and they suggested a number of possible neurophysiological mechanisms which might be involved. This observation of a diminished anxiety response in the schizophrenic patients can also be viewed as another example of the finding reported by numerous investigators of a decreased responsivity to a variety of experimental stimuli in chronic schizophrenic populations.

In the present instance it was observed that the schizophrenic patients were less able to cope with the experimental situation as a whole than were the "normal control" volunteers; and that they manifested a higher level of anxiety to the experimental situation, prior to the beginning of the epinephrine infusion, than did the "normal control" volunteers. This may be interpreted to suggest that in the schizophrenic patients the infused epinephrine was likely to constitute a proportionally smaller addition to the total circulating epinephrine (which would consist of the endogenously secreted plus the infused epinephrine) than was the case in the "normal control" volunteers and that this difference contributed substantially to the less marked anxiety reaction to epinephrine in the schizophrenic patients, as compared with the "normal control" volunteers.

In further evaluating the significance of the differences between "normal control" volunteer and schizophrenic patients' responses during this study, attention must be called to the several ways in which the two populations differed, apart from the presence or absence of schizophrenia. As shown in Table 1, and described above, they differed also with respect to age, schooling, length of stay at the National Institutes of Health prior to study, activity, prior relationship with the psychiatric investigators and other staff, and in familiarity with the ward on which the procedure was carried out. Among the "normal control" volunteers, all of whom lived on the same ward, there was a considerable amount of group interaction. When one of the "normal control" volunteers was notified of his participation in the study on the following day, there was a bantering but fundamentally supportive group response. Such group support did not occur amongst the schizophrenic patients. Another difference was the clear understanding, possessed by the "normal controls," of the purpose and goals of the study, in contrast to the varied pictures possessed by the schizophrenics, as to what was being done. Despite extended explanations, the schizophrenic patients' pictures ranged from the relatively clear, to the completely distorted and bizarre. There were also differences in the relationship established between the interviewing psychiatrists, and the subject, during each study.

VOL
1
1962

It is apparent that differences such as those itemized above will always be present when a study is undertaken comparing a schizophrenic and a "normal" population, and that the general tendency of such differences is to make the experimental variable play a less prominent role than is intended, especially for the schizophrenic population. It is felt that in such studies considerable efforts must be expended to define and, where possible, measure all such extraneous variables which cannot be eliminated, and in regard to which the schizophrenic and non-schizophrenic populations differ, and an attempt to evaluate their effect upon the experimental variable be made. Such an analysis, in this present study, will be presented in a fourth paper that will focus on intercorrelations of the data.

The literature dealing with the behavioral and central nervous system effects of epinephrine in man has recently been extensively reviewed[15]. A number of authors have dealt with the question of whether the anxiety which accompanies epinephrine administration is "true" anxiety, and conclude that it is not. [16–18] The present observations are compatible with these reports. Two "normal control" volunteers, more articulate and self-aware than most, did spontaneously distinguish between actual life-situation anxiety, and the subjective experience they were describing as anxiety accompanying epinephrine infusion. The distinction they drew was that though they had the usual physical accompaniments of anxiety — pounding heart, shaking limbs, tremulous voice — they did not actually feel "afraid." Though this question was not systematically pursued, other articulate, self-aware subjects were questioned along this line, and were unable to make any such distinction. In referring above to "overt anxiety" in response to epinephrine infusion, it is not implied that what was observed was identical with real life anxiety. It appears that the conclusion is warranted that in some individuals, at least, the affect "anxiety" produced by administration of epinephrine, is similar to, but not identical with, anxiety experienced in daily life. Although this likely distinction is granted, the similarities between these two states appear to be great enough to warrant lumping certain behavioral manifestations and subjective responses together as "overt anxiety."

The behavioral changes observed in this study as accompaniments of the epinephrine infusion have been previously observed by others. However, the fact that difficulties in communication and concentration may be amongst the most common effects of epinephrine, and the implications of these effects on an individual's ability to cope with the life stress situation which led to the secretion of large amounts of epinephrine is worthy of note. Though the heightened state of arousal can be seen as facilitating an individual's ability to cope with external stress, difficulties in concentration and communication, a narrowing of the field of external awareness[19] and a shift of attention to inner body processes, are all changes calculated to impede adequate interpretation of and response to a stressful environment.

SUMMARY

1. Twelve "normal control" volunteers and twelve chronic schizophrenic patients received intravenous infusions of isotopically labelled epinephrine in a complex experimental situation permitting simultaneous study of multiple biological and psychological variables.

2. The major psychological changes accompanying epinephrine infusion were: (a) in-

creased arousal, (b) narrowing of the field of attention, (c) change of direction of attention toward inner body experience, (d) resultant difficulty in communication and concentration and (e) subjective feelings of anxiety. Some "normal control" volunteer subjects distinguished these anxiety feelings from actual life-situation anxiety.

3. There was no qualitative difference in the psychological response of the schizophrenic and the "normal control" groups to epinephrine infusion. In neither "normal control" volunteers, nor schizophrenic patients, did epinephrine cause the appearance or exacerbation of psychotic symptoms. There were two instances of increase of psychotic behavior during or after the epinephrine infusion in schizophrenic patients, but these could not be attributed to the epinephine *per se;* and seemed more clearly related to situational variables. This result fails to support hypotheses which attribute the origin of schizophrenic symptoms to an abnormality in the metabolism of epinephrine.

4. Quantitative differences between the schizophrenic and "normal control" subjects showed that, as a group, the schizophrenic subjects were much less able to cope with the experimental situation ($p = <0{\cdot}002$), showed more anxiety in response to the situation ($p = <0{\cdot}02$) but less in response to epinephrine ($p = <0{\cdot}02$), and ranked lower on involvement–communication ($p = <0{\cdot}02$).

5. It is believed that a major factor in the smaller anxiety response during epinephrine infusion in the schizophrenic patient group, compared to the "normal control" group, was its higher situational anxiety baseline.

6. Differences between schizophrenic and "normal control" subjects in their ability to cope with an experimental situation, and in their resultant situational anxiety, are judged to be widely prevalent in research studies comparing schizophrenic and "normal control" subjects. Such differences must be given careful consideration before concluding that a particular hypothesis being investigated has or has not been validated.

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VOL. 1 1962

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OL.
1
62/63

THE PHYSIOLOGICAL AND PSYCHOLOGICAL EFFECTS OF INTRAVENOUSLY ADMINISTERED EPINEPHRINE, AND ITS METABOLISM, IN NORMAL AND SCHIZOPHRENIC MEN — III.

METABOLISM OF 7-H^3-EPINEPHRINE AS DETERMINED IN STUDIES ON BLOOD AND URINE

VOL.
1
1962/

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As a part of a collaborative study to investigate the psychological and physiological effects of epinephrine administration in normal and schizophrenic subjects[1,2] the metabolism of epinephrine was studied using epinephrine labeled with tritium.

Some evidence and considerable speculation has been developed in recent years which makes an examination of the metabolism of circulating epinephrine in schizophrenia of some interest at this time. Evidence of a diminished cardiovascular[3] and blood sugar[4] responsiveness to injected epinephrine on the part of schizophrenic patients, confirmed in another aspect of the present study[1], suggests a more rapid destruction of the hormone and a decrease in its concentration in the circulation as a possible explanation. A more rapid disappearance of epinephrine added *in vitro* to the serum of schizophrenic patients in comparison with normal serum[5] and its conversion to adrenolutin[6] has been reported. Psychotomimetic properties have been attributed to adrenochrome, adrenolutin or other oxidation products of epinephrine by some investigators[7,8] and have served as the chief experimental support of an interesting hypothesis which postulates an abnormality in the metabolism of circulating endogenous epinephrine as a significant factor in the pathogenesis of schizophrenia [9–11]. Although none of this evidence has gone unchallenged [12–15] the epinephrine hypothesis of schizophrenia was formulated at a time when the metabolism of this hormone was largely unknown and a crucial test of its validity unavailable. In the past 3 years, ARMSTRONG [16, 17] and AXELROD [18–21] and their respective associates have characterized the major and minor metabolic products of epinephrine, and the availability of stable, tritium-labeled hormone has made possible the practically complete accountability of injected epinephrine in terms of its several products[22] so that a comparison of the metabolism of this hormone in normal and schizophrenic subjects is possible.

OL. 1 62/63

TABLE 1. URINARY METABOLITES FOLLOWING INFUSION OF H^3-EPINEPHRINE IN SCHIZOPHRENIC PATIENTS

Patients No.	Total dose				% of inf. tritium excreted	Metabolites expressed as percentage of tritium in the urine										Total of metabolites
	L-epi.		D-epi.			Metanephrine				VMA	EPI	MHPG	DHMA			
	μg	μc	μg	μc		Free	Gluc.	"Sulfate"	Total				Free	Conj.	Total	
5*	765	142	255	142	85	6	7	18	31	39	7	8·3	0·43	0·68	1·11	86
4	1060	184	353	184	89	6	7	30	43	29	9	8·5	0·46	0·81	1·27	91
1	1040	180	347	180	84	6	6	25	37	36	7	9·1	0·64	0·75	1·39	90
6	652	166	217	166	78	4	9	23	36	44	5	6·4	0·89	1·49	2·38	94
10	645	308	645	308	77	5	18	44	67	47	2	11·8	0·71	0·71	1·42	129
3	508	233	508	233	87	4	15	33	52	39	6	11·3	0·16	0·82	0·98	109
12	337	197	337	197	87	9	7	14	30	41	8	6·8	0·56	1·53	2·09	87
2	343	146	343	146	98	8	8	14	30	35	6	7·6	1·14	0·52	1·66	80
7	331	162	28	162	115	4	4	39	47	38	7	9·7	1·56	0·43	1·99	104
11	486	113	0	0	100	6	10	36	52	43	8	7·9	0·94	0·80	1·74	113
9	434	210	434	210	74	6	8	33	47	24	4	11·2	0·73	0·90	1·63	88
8	361	177	361	177	67	6	7	35	48	35	10	8·2	1·24	1·78	3·02	104
Means					86·8	5·8	8·8	28·7	43·3	37·5	6·6	8·9	0·79	0·94	1·72	97·9
Standard Deviations					12·9	1·5	5·4	9·8	11·2	6·4	2·2	1·8	0·55	0·43	0·58	14·1

L-epi and D-epi = L- and D-epinephrine (free base)
Inf. = infused
Gluc. = glucuronide
VMA = 3-methoxy-4-hydroxymandelic acid
MHPG = 3-methoxy-4-hydroxyphenylglycol
DHMA = 3,4-dihydroxymandelic acid
Conj. = conjugated

* Patients are listed in the order in which they were studied. Corresponding data on the normal subjects have been reported elsewhere[33]

EXPERIMENTAL

Synthetic L-epinephrine to which was added DL-7-H^3-epinephrine was infused into twelve male schizophrenic patients ranging in weight from 63·5 to 120·1 kg at rates of 10·4 to 25·5 μg of L-epinephrine base per minute. (Total dose ranged from 331 to 1,060 μg L-epinephrine base and 113 to 616μc of H^3) as shown in Table 1. The studies in schizophrenic patients alternated with those in the normal controls[22].

Estimation of 7-H^3-epinephrine in blood and plasma

Samples of blood (17 ml) were withdrawn from the right femoral artery at 10, 20 and 29 minutes after the beginning of the epinephrine infusion and 1, 3, 5, 7, 15, 30 and 60 minutes following the end of the epinephrine infusion. Silicone-treated syringes containing about 0·05 ml of heparin solution (10 mg/ml) were used. The blood was transferred to silicone-treated beakers and 5·0 ml were transferred to centrifuge tubes containing 45·0 ml of 6% trichloracetic acid (TCA) solution and 1 mg of L-epinephrine-D-bitartrate which served to protect the tracer epinephrine against destruction. The tubes were shaken vigorously for 15–30 sec and the precipitated proteins were centrifuged down. 40 ml of the supernatant solution were transferred to a separatory funnel and extracted three times with 100 ml of peroxide-free ethyl ether*. 2 ml of 0·5 M sodium borate were added to the aqueous phase and this solution was adjusted to pH 8·3 (using a glass electrode) with 1 *N* NaOH. The resulting solution was passed immediately through a column of alumina (4 cm high, 1 cm diam.). Both Woelm non-alkaline and Bio-Rad basic alumina† were used with similar results. The alumina was washed with 20 ml of glass-distilled water, and the catechol amine fraction was eluted with four 5 ml portions of 1 *N* acetic acid. Triplicate 5 ml aliquots of the acetic acid eluate were lyophilized in scintillation counting vials‡. The residues were each taken up in 0·2 ml of 1 *N* acetic acid, 4 ml of ethanol and 10 ml of scintillator solution[23]. This mixture formed a thixotropic gel which was usually broken by shaking for several hours. The radioactivity was determined in a scintillation spectrometer.§

A tritium internal standard was added to each vial after the first counting run and a second series of counts determined. From these counts, after correction for background, the radioactivity (mμc) in the vials was calculated. Recovery of 7-H^3-epinephrine added to whole blood before precipitation by TCA was 84·1 ± 2·8% from the TCA precipitation, 87·7 ± 8·9% from the alumina column and 73·7 ± 7·4% overall recovery.

Twelve milliliters of the heparinized blood were centrifuged at 800 g for 10 min 5 ml of the supernatant plasma were transferred to a beaker containing 5 ml of 0·2 N sodium acetate and 1 mg of epinephrine bitartrate. The solution was adjusted to pH 8·3 with 6 *N* NaOH and was immediately transferred to an alumina column (4 cm high, 1 cm diameter) [24]. The beaker was rinsed four times with 5 ml of glass-distilled water and the rinsings were added to the alumina column. The catechol fraction was eluted with four 5 ml portions of 1 *N* acetic acid and processed for determination of the radioactivity as described above. The overall recovery of 7-H^3-epinephrine, added to fresh plasma and processed by this procedure, was 78·4 ± 4·1%.

The specificity of this procedure was checked on blood from cats which were given relatively large doses of 7-H^3-epinephrine. These blood specimens had been found to contain metanephrine and 3-methoxy-4-hydroxymandelic acid as well as unchanged epinephrine. However, the lyophilized acetic acid eluates showed only one peak of radioactivity which corresponded to authentic epinephrine.

The methods for the estimation of the urinary metabolites of 7-H^3-epinephrine have been described in detail elsewhere[22]. Briefly they are as follows‖—

* The peroxides were removed by passing the ether through a 5 cm column of activated basic alumina (Woelm); when not used immediately it was stored over a layer of water.

† Preparation of the alumina. The alumina was stirred with glass-distilled water several times, and the fine particles remaining in suspension after 10 min were decanted. The washed alumina was filtered on a Buchner funnel and dried overnight at 110°C. The alumina was packed into the columns either as a dry powder or as a slurry in pH 8·3 borate buffer.

‡ Wheaton Glass Company, Millville, New Jersey.

§ Packard Tri-Carb Scintillation Spectrometer, LaGrange, Illinois.

‖ All estimations of radioactivity were made by adding aliquots of the urine or extracts to a scintillator solution which contained 4 ml of ethanol, and 10 ml of toluene containing 0·01% β-bis [2(phenyloxazolyl)] benzene and 0·4% 2,5-diphenyloxazole. The toluene with fluorescent solutes is called the fluor solution in this paper.

VOL. 1 1962

Total urinary radioactivity. This was estimated by counting 0·1 ml portions of urine in the ethanol–fluor solution.

Free H^3-metanephrine. This was estimated by extraction of an aliquot of the urine with *iso*amyl alcohol after adjusting to pH 10. Aliquots of the *iso*amyl alcohol extracts were added to vials containing the scintillator solution.

H^3-Metanephrine glucuronide. This was estimated by adjusting an aliquot of the urine to pH 6·5 and incubating with bacterial β-glucuronidase. The hydrolized urine was adjusted to pH 10, extracted, and the radioactivity was estimated as above for the free H^3-metanephrine. Since this extract contained both fractions, the value for H^3-metanephrine glucuronide was obtained by subtracting the value for free H^3-metanephrine.

H^3-Metanephrine sulfate. This was estimated by adjusting the urine to a final concentration of 1 *N* with HCl and heating in a water bath at 37°C for 48 hr. After this acid hydrolysis the urine was adjusted to pH 10, extracted, and an aliquot of the *iso*amyl extract was counted as above. This extract contained free H^3-metanephrine sulfate, only negligible amounts (4%) of the H^3-metanephrine glucuronide have been found to be hydrolized under these conditions. The H^3-metanephrine sulfate in the extracts is calculated by subtracting the value for free H^3-metanephrine.

7-H^3-3-methoxy-4-hydroxymandelic acid (H^3-VMA). H^3-VMA in the urine was estimated by adjusting an aliquot of the urine to pH 1 and extracting with *iso*amyl alcohol. The H^3-VMA was extracted from the *iso*amyl alcohol into 5% sodium bicarbonate solution. The sodium bicarbonate extract was adjusted to pH 1 and extracted with fresh *iso*amyl alcohol. The radioactivity in an aliquot of the final *iso*amyl alcohol extract was estimated.

7-H^3-3-methoxy-4-hydroxyphenylglycol (MHPG). MHPG in the urine was estimated* by adjusting an aliquot of the urine to pH 11 and precipitating the inorganic phosphate and sulfate with saturated $BaCl_2$ solution. The precipitate was centrifuged and the supernatant solution was adjusted to pH 6·5 and incubated with sulfatase† for 24 hr. The hydrolyzed urine was centrifuged and supernatant solution was passed through a column of Dowex 50 cation exchange resin. The column was washed with water and the effluent and washings were combined, saturated with NaCl, adjusted to pH 6·5 and extracted with ethyl acetate. The ethyl acetate extract was evaporated and the residue was dissolved in ethanol. An aliquot of the ethanol was added to the toluene–fluor solution and the radioactivity was counted.

H^3-Epinephrine. H^3-Epinephrine in the urine was estimated by chromatography of the urine on alumina and elution by 1 *N* acetic acid. The acetic acid eluate was lyophilized and the radioactivity was estimated by dissolving the residue in 0·2 ml of 1 *N* acetic acid, adding 14 ml of the ethanol–toluene–fluor solution and counting.

Free 7-H^3-3, 4-Dihydroxymandelic acid (DHMA). DHMA was estimated* by adjusting an aliquot of the urine to pH 8·4 followed by chromatography on alumina. The alumina was washed with water and the free catechols were eluted with 0·2 *N* H_2SO_4. The sulfuric acid eluate was extracted with ethyl acetate. The ethyl acetate extract was evaporated to dryness *in vacuo* and the residue was dissolved in the ethanol–fluor solution and the radioactivity was counted as above.

Conjugated 3,4-dihydroxymandelic acid. This was estimated* in the combined effluent and washings of the alumina column by acid hydrolysis, readjustment to pH 8·4, chromatography on alumina, extraction, concentration and counting as above for free DHMA.

RESULTS

The blood and plasma levels of epinephrine showed a tendency to reach a plateau 10–20 min after the beginning of the infusion period (Fig. 1). Following the cessation of the infusion the blood epinephrine levels show a rapid decrease for the first 7 min post-infusion, followed by a slow decrease thereafter.

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* These analyses were performed by Dr. I. J. Kopin with the assistance of Edna Gordon.

† Glusulase, Endo Products, Inc., New York.

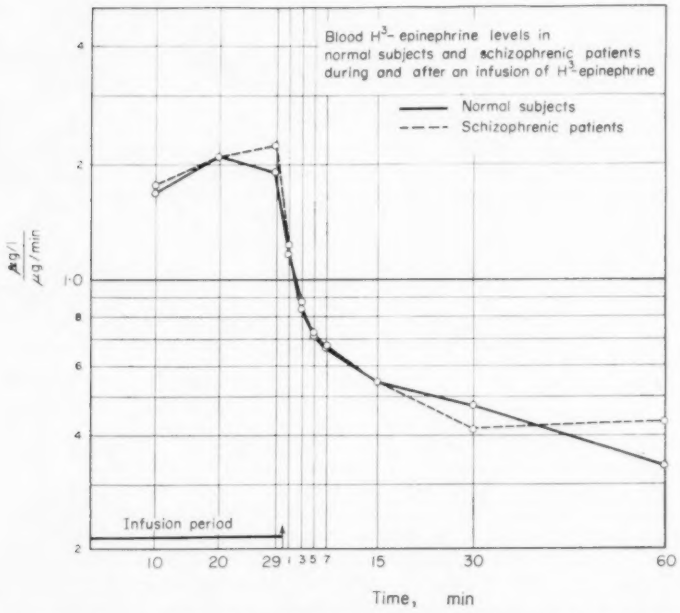
Blood H³- epinephrine levels in normal subjects and schizophrenic patients during and after an infusion of H³-epinephrine
Normal subjects
Schizophrenic patients
μg/l / μg/min
Infusion period
Time, min

FIG. 1. Comparison of average blood levels of H^3-epinephrine (corrected for infusion rate) for 12 male schizophrenic patients (– – – – –) and 12 normal male subjects (————) during and for 1 hr after giving an intravenous infusion of DL-H^3-epinephrine-D-bitartrate. The average values at 29 min after the beginning of the infusion, and at 30 and 60 min post infusion have standard errors of 0·12, 0·06 and 0·05 respectively for normal subjects and 0·23, 0·12 and 0·11, respectively, for the schizophrenic patients. The means at each of these points are not significantly different from each other (t values are 1·23, 0·40 and 0·09; P values are $0·25 > 0·5$ and $> 0·5$, respectively).

In Fig. 1 the mean plasma levels (corrected for infusion rate) of the schizophrenic patients are graphed with those of normal subjects; no significant difference is present between the means of these groups.

The percentage of the infused tritium which was recovered from the fifty-four-hour urine amounted to 86·8%. The catechols, constituting 8·3% of the tritium in the urine, were made up of free epinephrine (6·6%) and 3,4-dihydroxymandelic acid (1·7%). The 3-methoxy metabolites totaled 89·7%; these were free and conjugated metanephrine (43·3%), 3-methoxy-4-hydroxymandelic acid (37·5%), and 3-methoxy-4-hydroxyphenylglycol (8·9%). The percentage of tritium in the urine represented by each of the H^3-epinephrine metabolites for each one of the patients is shown in Table 1.

DISCUSSION

In this study two parameters of epinephrine metabolism were measured, the blood levels of H^3-epinephrine during and after cessation of the H^3-epinephrine infusion and the urinary excretion of tritium-labeled epinephrine metabolites.

No significant difference in epinephrine blood levels during or after the infusion period

was found between the schizophrenic patients and normal human subjects, confirming the findings of COHEN and associates[25], who infused unlabeled epinephrine into similar populations. However the present findings differ from theirs in certain other respects probably on the basis of a greater sensitivity made possible by the use of the isotopic label and by sampling from an artery rather than from an antecubital vein. Whereas the previous study yielded evidence for only a single exponential loss of epinephrine from the blood, the present data show clear evidence for at least two phases in this process, a rapid decay with a half life of 1·2 min, and a considerably slower one with a half life of 75·3 min, consistent with the heterogeneity in distribution of blood to various tissues and the binding and slow release of epinephrine in certain tissue depots[26].

The more rapid degradation of epinephrine, reported by some, after its addition *in vitro* to the serum of schizophrenic patients[5] has been shown by MCDONALD[15] and others[27] to be attributable to failure to control dietary and blood levels of ascorbic acid. The present findings fail to support the thesis that a more rapid degradation of epinephrine occurs *in vivo* in chronic schizophrenic patients as compared with the normal.

OL.
1
62/63

TABLE 2. COMPARISON OF URINARY METABOLITES BETWEEN NORMAL SUBJECTS AND SCHIZOPHRENIC PATIENTS AFTER INFUSION OF H^3-EPINEPHRINE

	Normals	Schizophrenics
Metanephrine	(12 Subjects)	(12 Patients)
Free	5·2 ± 1·1%	5·8 ± 1·5%
Glucuronide	6·0 ± 1·5	8·8 ± 5·4
Sulfate	29·5 ± 9·0	28·7 ± 9·8
Total	40·8 ± 9·5	43·3 ±11·2
3-Methoxy-4-Hydroxymandelic Acid	41·2 ± 8·4	37·5 ± 6·4
Free Epinephrine	6·8 ± 1·5	6·6 ± 2·2
3-Methoxy-4-Hydroxyphenylglycol	7·1 ± 1·4	8·9 ± 1·8
Dihydroxy-mandelic Acid		
Free	0·66 ± ·31	0·79 ± ·55
Conjugated	0·93 ± ·38	0·94 ± ·43
Total	1·59 ± ·57	1·72 ± ·58
Total percent R.A. in urine accounted for by the above metabolites	97 ± 14	98 ± 14
Percent of Infused R.A. excreted in the urine	93 ± 8	87 ± 13

An analysis of variance on these data revealed no significant difference between groups ($F = 0·002$).

Since the blood levels achieved in equivalent infusion rates were the same for both normal and schizophrenic patients, differences in response to epinephrine between the two groups cannot be explained on the basis of differences in the rate of removal of the hormone from the blood.

Even though no difference was observed in the rate of clearance of epinephrine from the blood, the possibility still existed that the pathways of metabolism of epinephrine might be different between the normal subjects and the schizophrenic patients. The urinary metabolites were studied to examine the possibility of a difference in the metabolism. Comparison of the tritium-labeled metabolites of the normals and schizophrenic patients is shown in Table 2. All of the metabolites were excreted to practically the same extent by each of the groups and 97 to 98% of the urinary tritium is accounted for in terms of the metabolites studied. These findings indicate that in addition to the similarity in the rate of clearance of H^3-epinephrine from the blood, there is also essentially no difference in the pattern of urinary metabolites between the schizophrenic patients and the normal subjects.

After the intraperitoneal administration of 7-H^3-adrenochrome[28] to animals the urinary metabolites are different from those excreted after the administration of 7-H^3-epinephrine. This finding, plus the finding that only 2% of the urinary tritium remains unaccounted for after the intravenous administration of 7-H^3-epinephrine, indicates that practically none, if any, of the infused epinephrine could have been metabolized via adrenochrome or its products either in normal subjects or schizophrenic patients.

The close agreement between the disappearance of 7-H^3-epinephrine from the blood and the pattern of the urinary metabolites between normal subjects and schizophrenic patients argues against the presence of a major quantitative or qualitative abnormality in the metabolism of circulating epinephrine in schizophrenia.

VOL.
1
1962/

SUMMARY

As part of a collaborative study, blood levels and urinary metabolites of H^3-epinephrine were measured in twelve schizophrenic and twelve normal males during and up to one hour following the intravenous infusion of DL-7-H^3-epinephrine-D-bitartrate. The plateau levels and the rate of decrease in blood levels of labeled epinephrine after stopping the infusion showed no significant differences between the groups. The following tritium-labeled metabolites in the urine were assayed and found to account for 97 to 98% of the urinary tritium in each group — Metanephrine, free and conjugated, 3-methoxy-4-hydroxymandelic acid, 3-methoxy-4-hydroxyphenylglycol, free and conjugated 3,4-dihydroxymandelic acid and unchanged epinephrine. An analysis of variance on the data for the urinary metabolites showed no significant difference between the normal subjects and the schizophrenic patients. The agreement between the findings on normal subjects and schizophrenic patients argues against the possibility of a major abnormality in the metabolism of circulating epinephrine in schizophrenia.

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A DOUBLE-BLIND COMPARISON OF PLACEBO AND IMIPRAMINE IN THE TREATMENT OF DEPRESSED PATIENTS IN A STATE HOSPITAL*

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VOL. 1 1962

IN 1957 KUHN described the beneficial effect of imipramine (Tofranil) on patients with depression.[1] Since then a number of favorable reports have been published emphasizing the effectiveness of imipramine in depressive states, particularly in psychotic or endogenous depressions.

In this study the effect of oral imipramine was compared with that of placebo, in a double-blind controlled trial, in patients admitted to a state hospital with a diagnosis of "psychotic depressive reaction". The basic plan of the study was to have a total observation period of 8 weeks with half of the patients to be placed on imipramine for 4 weeks and then placed on placebo, and the other half to receive placebo first and the active medication in the second 4-week period. The changes in the patients were recorded on a rating scale, with the total scores used to follow overall change and sub-groups of the scale used to measure changes in certain symptoms.

SETTING

Springfield State Hospital has a capacity of 3,500 beds, is built in cottage style, and is situated 24 miles from the city of Baltimore. All newly admitted patients were treated in the closed and architecturally old admission ward together with other patients not involved in this study. The patients remained here until they were evaluated and considered to be safe in an open ward. The ratio† of nursing personnel to patients in this ward is 1 : 2·3. As soon as patients showed sufficient improvement they were transferred to the open convalescent or geriatric cottages, following the usual routine of the hospital. On all of the wards patients were under the general care of the ward physician who gave privileges and weekend leaves and ordered transfers to open wards according to his

* Supported in part by a grant [B–865 (C3)] from the National Institutes of Health. This study was conducted at Springfield State Hospital, with the assistance of the staff.

† The ratios given in this paragraph are based on the total number of attendants per ward over a 24-hour period, a figure which is three times the average number of attendants on duty at any given time.

judgment. The ward physician could also decrease or discontinue the experimental drug and prescribe medications for physical ailments, but was not permitted to prescribe any neuroleptic medication. Like other patients, those included in the study attended occupational and recreational therapy and were encouraged to participate in work therapy, but none received individual psychotherapy. The attitude of the medical staff and nursing personnel was generally that of great interest and at times, enthusiasm, a factor making the double-blind technique even more important. The medical staff members involved in the study did not adhere to any extreme school of therapy nor did they restrict themselves in psychiatric therapy to any one form of psychiatric treatment.

OL.
1
62/63

SELECTION OF PATIENTS AND DIAGNOSTIC CRITERIA

Patients were selected who, on admission, suffered from depression and were considered psychotic. The evaluations were confirmed by at least two senior psychiatrists. Some patients in whom this diagnosis was not certain were included and reassessed later (see below). Since diagnostic criteria vary greatly from hospital to hospital, a brief outline of the criteria employed is perhaps in order. Any major depression with retardation or absence of agitation, with no overt anxiety was diagnosed as "psychotic depressive reaction". The classification "involutional psychotic reaction" was used in cases where the first depressive episode began in the involutional period and was associated with overt anxiety, agitation, and morbid thoughts.

The differentiation of psychoneurotic disorder, depressive reaction, from psychotic depressive reaction was based on the past history, the dependence of the depression on external factors, the responsiveness to environment as expressed by the patient's accessibility to reassurance, by the less protracted course, and by the absence of typical diurnal fluctuation and malignant symptoms. The patients diagnosed as neurotic depression were included in this study because the medical staff disagreed initially on the diagnosis. Similarly some patients with the final diagnosis of schizophrenic reaction were first tentatively diagnosed as depressions since they manifested depressive mood changes without clear schizophrenic symptomatology. Such patients were considered borderline cases in the initial period of evaluation, but the later appearance of more definitive symptoms led ultimately to the diagnosis of schizophrenia which was made independent of the final results of the treatment and without breaking the drug code.

The general diagnostic criteria were based on the "Diagnostic and Statistical Manual, Mental Disorders, APA 1952", with the exception that the one manic depressive patient in our study was added to the group of psychotic depressive reactions.

Most of the new admissions were observed for 1–3 weeks before they were placed into the study. None of the patients had received any physical treatment for several months before the study with the exception of one patient who had had electric shock shortly before admission and who was later diagnosed as schizophrenic. Patients with such disabilities as cardiac decompensation, recent cardiac infarct, severe liver or kidney disease, or epilepsy were excluded.

The diagnosis, sex, age, duration of illness, length of hospitalization, and previous major

psychiatric history of the thirty-two patients studied are given in Tables 1A and 1B. The patients were predominantly of the lower socio-economic and educational strata, none were mentally defective, all were white.

METHOD OF ADMINISTRATION OF TREATMENTS

All patients were placed either on active drug or on placebo identical in appearance to the drug in a randomized block design. The separate code numbers for all patients were known only to one of the investigators, who was involved neither in the selection nor in the evaluation of the patients. All medication was given by mouth starting with one tablet four times a day (25 mg per tablet in the case of imipramine) and systematically increasing the dosage within the first week of observation. At the beginning of the study the dosage was increased to a maximum of four tablets four times a day (400 mg per day of imipramine), the dose to be decreased if disturbing side reactions appeared. However, because of several serious toxic reactions early in the study it was decided not to exceed 200 mg in the cases treated thereafter.

The patients were told that they were receiving a new drug which had been found to be beneficial to some cases of disease similar to theirs, but that a definite favorable response to the drug could not be guaranteed in any specific case. The explanation was deemed necessary because of the frequent blood pressure readings, laboratory tests, and regular interviews with an outside psychiatrist. The nursing personnel were told that two new antidepressants were to be given and were not aware of the fact that any patients were to receive placebo.

After 4 weeks on one treatment the patients were placed on the alternate medication. To avoid unpleasant reaction due to a sudden high dosage of active medication it was necessary to start again in all cases with a low dosage. Most of the patients did not suspect the change of medication, believing only that the dosage had been readjusted; however, some of the patients, noticing side effects, suspected that they were receiving a new drug.

No other medication was given except barbiturates at bed time in a few extreme cases and indicated drugs such as insulin for diabetes and antibiotics for infections.

Not all of the patients completed the 8-week investigation. Eight (one patient on placebo, the others on imipramine) left the hospital against advice or required discontinuation of therapy. (See Table 1A and 1B.)

EVALUATION OF CHANGES

Patients were evaluated by a physician on a rating scale (see Appendix I) which was designed to break down the general picture of depression into categories such as mood, pathologic thinking etc., and these categories into single items which could either be objectively observed or subjectively reported by the patients. To avoid variations in rating due to inter-rater differences, all patients were seen by the same psychiatrist in half-hour interviews before any medication was given and then at weekly intervals while on treatment. This psychiatrist was not on the staff of the hospital. In addition every nursing shift made separate short notes on the patients and the ward physician gave global impressions of the patients at irregular intervals. These sources of information were also used by the psychiatrist in his ratings.

VOL.
1
1962/

PSYCHOL.
1
62/63

Table 1A. Effects of placebo and imipramine in individual patients

No.	Diagnosis	Sex–age	Duration present illness	Length of hospitalization	Previous major psychiatric illnesses	Pre-treatment score*	Total score 4th wk placebo**	Total score 8th wk imipramine***	Reason for discontinuation
1	Psychotic depressive reaction	M–65	7 mth	20 days	None	27	18	2	
2	,,	M–39	2 yr	7 days	None	16	8	1	
3	,,	M–31	5 mth	8 days	"Nervous breakdown" in army, 1947	28	5	1	
4	Psychotic depressive reaction – Chronic brain syndrome	F–59	8 mth	30 days	None	20	29	34	
5	,,	F–72	8 days	7 days	Depression not classified, 1927–1946	24	9	0	
6	Involutional psychotic depressive reaction	F–54	4 yr	19 mth	None	31	27	22	
7	,,	F–63	10 mth	11 days	None	23	1	1	
8	,,	M–63	2 mth	11 days	None	10	15	0	
9	,,	M–63	14 mth	9 days	None	17	13	1	
10	,,	F–57	12 mth	3 days	"Nervous breakdown", 1922	30	30	—	Discharged on family's request
11	Neurotic depressive reaction	F–48	6 yr	15 days	None	17	2	9	
12	,,	F–39	2 yr	30 days	None	9	14	1	
13	,,	F–55	7 mth	7 days	None	12	2	0	
14	Schizophrenic depression	M–34	21 days	5 days	None	29	21	27	
15	,,	M–44	2 yr	1 mth	Schizophrenic reaction, 1944–1954	37	33	29	
16	,,	F–48	1 yr	17 days	Diagnosis unknown, 1930	24	12	26	

* The higher the score, the greater the degree of psychopathology (Max 60)

** Score after 4 weeks on Placebo.

*** Scores 4 weeks after patient was switched to imipramine.

TABLE 1B. EFFECTS OF IMIPRAMINE AND PLACEBO IN INDIVIDUAL PATIENTS

No.	Diagnosis	Sex—age	Duration present illness	Length of hospitalization	Previous major psychiatric illnesses	Pre-treatment score*	Total score 4th wk imipramine**	Total score 8th wk placebo***	Reason for discontinuation
17	Psychotic depressive reaction	F–60	1 mth	7 days	Depression, type unknown, 1940	22	13	20	
18	,,	F–49	7 mth	9 days	None	21	1	1	
19	,,	M–51	6 wk	7 days	None	12	1	—	Discharged on family's request
20	Manic depressive reaction	F–50	7 mth	15 days	Same diagnosis, 1945, 1947, 1954, 1955, 1957	31	4	18	
21	Involutional psychotic depressive reaction	F–59	6 mth	21 days	None	25	5	9	
22	,,	F–52	2 mth	10 days	None	27	4	3	Toxic psychosis†
23	,,	F–57	2 mth	7 days	Same — 1954	33	6	10	
24	,,	F–68	2 yr	1 yr	None	35	35	—	Severe anorexia
25	,,	M–63	1 yr	14 days	None	30	30	9	
26	,,	M–64	8 mth	8 days	None	23	9	21	
27	,,	M–64	2 yr	5 days	None	27	27	—	Manic state
28	,,	M–52	4 mth	5 days	None	27	27	—	Toxic psychosis
29	Neurotic depressive reaction	F–38	1 yr	4 mth	Same — 1940	23	23	—	Severe agitation
30	,,	F–40	3 mth	8 wk	Same — alcoholism, 1956	29	12	3	
31	Schizophrenic depressive reaction	F–59	4 mth	8 days	Schizophrenic reaction, 1924–28	32	8	—	Pneumonia
32	,,	F–56	2 mth	3 days	Schizophrenic reaction, 1937, 1943	25	25	—	Severe agitation

* The higher the score, the greater the psychopathology (Max 60).
** Score after 4 weeks on imipramine.
*** Score 4 weeks after patient was switched to placebo.
† Discontinued temporarily.

VOL. 1 1962

Patients were also rated by the ward personnel on a Ward Behavior Rating Scale which was filled out independently by the nursing personnel who were in constant contact with the patient and which was not available to the psychiatrist. Simple terms were used describing spontaneous behavioral patterns and needing little interpretation. Seventeen sections of descriptive terms were used to determine observable factors, such as: self-care, alertness and interest, behavior towards fellow patients and personnel, activity, mood, sleeping and eating habits, somatic complaints, expression of delusional thinking and of suicidal preoccupation. Each section contained five items, ranging in value from 1 to 5 (e.g., *Self-care:* 1, takes care of himself; 2, takes poor care of his clothing; 3, neglectful in eating habits; 4, poor personal hygiene — bathing, washing, cleaning teeth; 5, soils. *Mood:* 1, friendly and outgoing; 2, appears serious and lost in thoughts; 3, says he feels blue; 4, says he feels unhappy; 5, says he feels desperate). The rater was allowed to underline any term which applied to the patient's behavior, even several in the same section. The score of each section was equal to the numerical value of the highest underlined item. A total score of seventeen was considered "normal", of eighty "most deviant".

OL.
1
62/63

LABORATORY WORK

Blood pressure was taken thrice daily for the first 3 days and once daily thereafter if no gross fluctuations occurred. Weight, white cell count (with differential), red blood cell count, thymol turbidity, icterus index and urinalysis were recorded at weekly intervals throughout the study.

RESULTS

1. *General*

The plan to use "each patient as his own control," originally selected because of the paucity of severely depressed patients, proved to be of limited utility. There was, for example, a differential drop-out of patients, with seven patients who started on drug failing to enter the placebo period and only one patient originally started on placebo failing to enter the drug period.

The analysis which seems most appropriate is one based on the first 4 weeks of treatment only, which provides sixteen patients per treatment. This small number is further diminished by the need for stratifying the population into several types of depression, since imipramine has been alleged to be more useful in certain types of depression than in others. The consequence of the above is to make it difficult to pick up drug–placebo differences, so that this part of the report is essentially one on the methodology of antidepressive drug studies rather than a definitive assessment of imipramine.

2. *Physician's ratings*

The results of the ratings made by the psychiatrist are summarized in Tables 1A, 1B, 2 and 3. It will be seen that there is little difference between imipramine and placebo in the averages for all cases whether one looks at total scores, or the component mood, psychomotor activity, pathological thinking, somatic symptoms, or sleep scores. The general pattern was one of gradual improvement (i.e., decrease in scores) over time. There

TABLE 2. PHYSICIAN'S RATING SCALE: TOTAL SCORES* (MAX = 60)

Patients	Pre-Rx	1st wk	2nd wk	3rd wk	4th wk
Placebo (N = 16)					
All cases	22·1	16·6	16·3	16·3	14·9
Psychotic (N = 5)	23·0	16·6	15·0	15·6	13·8
Involutional (N = 5)	22·2	18·8	20·4	19·4	17·2
Neurotic (N = 3)	12·7	5·7	5·0	6·3	6·0
Schizophrenic (N = 3)	30·0	23·7	23·0	22·0	22·0
Imipramine (N = 16)					
All cases	26·4	19·8	17·4	16·3	14·4
Psychotic (N = 4)	21·5	17·3	13·0	8·5	4·8
Involutional (N = 8)	28·4	21·8	19·1	19·8	17·9
Neurotic (N = 2)	26·0	18·5	18·5	18·0	17·5
Schizophrenic (N = 2)	28·5	18·5	18·5	16·5	16·5

* The higher the score, the greater the degree of psychopathology.

TABLE 3. PHYSICIAN'S RATING SCALE: FIRST AND LAST RATINGS FOR MOOD, PSYCHOMOTOR ACTIVITY, PATHOLOGICAL THINKING, SOMATIC COMPLAINTS AND SLEEP

	No.	Mood score (Max = 15)		Psychomotor score (Max = 9)		Pathological thinking (Max = 15)		Somatic score (Max = 16)		Sleep score (Max = 3)	
		Pre-Rx	4th wk	Pre-Rx	4th wk	Pre-Rx	4th wk	Pre-Rx	4th wk	Pre-Rx	4th wk
Placebo											
All cases	16	7·1	4·3	1·8	1·0	4·2	2·3	5·0	4·4	1·8	1·1
Psychotic	5	8·0	3·8	1·4	0·6	5·2	2·4	4·8	3·8	1·2	1·4
Involutional	5	7·4	5·4	2·2	1·8	3·2	2·0	4·8	4·6	2·0	1·6
Neurotic	3	5·0	2·0	0·7	0	1·3	0·7	3·3	2·3	1·7	0
Schizophrenic	3	7·3	5·6	2·6	1·3	7·0	3·7	7·3	7·3	2·3	0·7
Imipramine											
All cases	16	8·3	4·4	1·6	0·7	5·1	2·8	7·0	3·9	1·9	0·8
Psychotic	4	7·5	1·8	1·3	0	4·3	1·0	4·8	1·3	1·8	0·3
Involutional	8	7·8	4·6	1·6	1·0	5·9	3·6	8·5	5·8	1·9	0·9
Neurotic	2	9·5	2·0	1·5	0·5	3·0	2·0	6·5	3·5	2·5	1·5
Schizophrenic	2	10·5	6·5	2·0	1·0	5·5	4·0	6·0	2·5	1·5	1·0

VOL. 1 1962/

are some suggestive differences in the stratified scores. On all mean scores psychotic depressions improved more under imipramine than under placebo, but the results in other categories were less clear-cut. All these scores are in a sense misleading, however, because they combine improvement, no change, and deterioration; because the small numbers in the subgroups allow for undue weighting by single cases, and also because they arbitrarily use, for patients withdrawn from the trial for reasons of toxicity or worsening of clinical state, the original pretreatment scores for all scores missing because of failure to complete the trial. For these reasons, the data are also presented for individual patients in Tables 1A and 1B and as percentage changes from pretreatment level in Table 4. Here it will be seen

Table 4. Per cent change in total scores at end of 4-week period of treatment

Change	Psychotic	Involutional	Neurotic	Schizophrenic
Placebo				
Improvement 75–100%	1	1	2	—
50– 74%	2	—	—	1
25– 49%	1	—	—	1
No change (<25%)	—	3	—	1
Deterioration 25–49%	1	—	—	—
50%+	—	1	1	—
Imipramine				
Improvement 75–100%	3	3	—	1
50–74%	—	1	1	—
25–49%	1	—	—	—
No change (<25%)	—	2	1	1
Deterioration 25–49%	—	—	—	—
50%+	—	—	—	—
Improved but failure due to toxicity	—	2	—	—

that in the psychotic and involutional depressions, although placebo administration was associated with occasional dramatic improvement, the percentage of dramatic improvement in the drug-treated group was higher. No method of analysis provides any convincing

evidence for differential therapeutic benefit from drug in the neurotic or schizophrenic groups, and indeed even in the group of endogenous depressions, the placebo–drug differences do not yield statistical significance at the 5% level.

3. *Ward ratings*

These are not presented in detail because of certain gaps in the data which make mathematical analysis difficult. In comparisons of the final global judgments (as to improvement, no change, or deterioration) of the psychiatrist and the ward personnel, however, it was found that the relative performance of imipramine and placebo was similar by both techniques, but that there was a definite inclination for the ward observers to report more therapeutic benefits from both placebo and drug (see Table 5).

TABLE 5. COMPARISON OF RATINGS OF PSYCHIATRIST AND WARD OBSERVERS

Category	Total No. of ratings	No. of ratings in which ward scores show more "optimistic" evaluation
I Exact agreement	24	—
II Discrepant ratings		
A. Both show improvement, but of different degrees	14	11
B. One shows no change; other shows improvement	14	10
C. One shows no change; other shows deterioration	3	1
D. One shows improvement; other shows deterioration	5	4
Total of discrepant ratings	36	26

4. *Treatment of "failures"*

The original design of the experiment did allow for some observations on the treatment by a second agent of patients who had failed to show significant improvement during the first 4-week period. Thus of nine patients who were considered to have "failed" (i.e., who showed no change, deterioration, or suboptimal improvement) on placebo (Patients 1, 4, 6, 8, 9, 12, 14, 16) four showed marked improvement during the four subsequent weeks

on imipramine (see Table 1A). However, of three patients who "failed" on imipramine (Patients 17, 25, 30), one subsequently showed moderate and one marked improvement on placebo (see Table 1B). The assumption that a patient who has not responded to one course of treatment is necessarily a more difficult therapeutic challenge is thus not borne out by the results in this study.

5. *Laboratory findings*

No abnormalities were detected in the functions followed except for alterations in the white blood count. Eosinophil counts of 5% or more were considered to indicate an eosinophilia. 18% of the patients on placebo showed eosinophilia whereas 37% of those on imipramine did. One patient on imipramine showed a rise in total W.B.C. to 20,000, with an eosinophilia of 30% on the eighteenth day of drug treatment, and 37% on the twentieth day. There were no other evidences of toxicity in this patient, whose discharge against medical advice precluded follow-up on the hematologic abnormality. One other patient showed a gradual decrease of total W.B.C. on drug from 6000 to 3700 but in this case also discharge prevented follow-up studies.

Urinalyses revealed no abnormalities.

OL.
1
62/63

6. *Blood pressure*

During the study it appeared that the primary changes related to the drug were decreases in blood pressure. Systolic pressure was predominantly affected, diastolic pressures showing little or no change. Of twenty-five patients on whom data were available, nine showed decreases in blood pressure of less than 20 mm Hg, five showed a decrease of 20–40 mm Hg, and one showed a drop exceeding 40 mm Hg. Five additional patients showed considerable fluctuation in blood pressure, without a consistent pattern. Of these, four showed fluctuations of 20–40 mm Hg, and one of over 40 mm. Four other patients showed similar fluctuations, but the readings while on drug were essentially the same as those on placebo. Only one patient showed a rise in blood pressure of over 20 mm Hg on drug. In some patients, the initial drop of blood pressure seemed to diminish as drug was continued. A few patients complained of dizziness on standing or after physical exertion. Other than the fluctuations in pressure already mentioned, no significant blood pressure changes were observed during placebo therapy.

7. *Other side effects*

The reported incidence of side effects is seen in Table 6. It appears that certain side effects are more prominent on drug than on placebo. These include dryness of the mouth, fine tremor, increased tension, increased perspiration, jerking movements of the trunk or limbs, dizziness, blurred vision and nausea.

Two patients suffered an acute toxic psychosis on drug. One, a 52-year-old male with the diagnosis of involutional psychosis, became dizzy, nauseated, and complained of headache on the third day, when the dose was 200 mg/day. On the fifth day, on 400 mg/day,

he had a transitory hallucinatory episode with confusion. Despite reduction in dosage to 300 mg/day, he developed a typical toxic psychosis on the seventh day, with disorientation, agitation, ataxia, profuse perspiration, picking movements of the fingers and visual hallucinations. Drug was stopped and on the next day the patient, although still complaining of

TABLE 6. NUMBER OF PATIENTS WITH SIDE EFFECTS

Side Effect	Imipramine (N=31)	Placebo (N=24)
Headache	14	17
Nausea	5	1
Vomiting	2	1
Anorexia	2	0
Dizziness	6	1
Dry mouth	25	5
Blurred vision	5	0
Palpitation	4	6
Fine tremor	16	5
Increased tension	10	3
Jerking movements	8	0
Increased perspiration	8	3
Constipation	7	11
Tinnitus	3	0
Rash	2	1
Severe agitation	2	0
Acute toxic psychoses	2	0
Acute emergence of previously masked schizophrenic symptoms	2	0
Mania	1	0

nausea, vomiting, headache, perspiration, tension and malaise, and exhibiting amnesia for the previous 2 days, was oriented and in good contact with his environment. A week later imipramine was started at a dose of 100 mg/day. The patient reacted promptly with nausea, vomiting, perspiration, tension, and malaise, and the drug was discontinued.

The second patient, a 52-year-old female with the diagnosis of involutional psychosis, developed nausea, vomiting, agitation, insomnia, and hostility on the third day (dose of 200 mg/day). The dose was halved to 100 mg/day but 2 days later the patient showed nausea, disorientation, picking movements and visual hallucinations, and conversed with imaginary people. Within a day of stopping drug the patient returned to her pre-drug state, although there was amnesia for the period of toxic psychosis. After one week, drug was restarted at 100 mg/day and gradually increased to 200 mg/day. The medication was well tolerated, and the patient improved on drug.

One patient, a 64-year-old involutional psychotic, became manic in the third week of drug treatment, at a dose of 400 mg/day. He was kept off drug for 6 weeks, during which time the manic state subsided slowly.

VOL. 1 1962/

The rashes in two patients disappeared within a few days despite continued medication, and were probably not drug-related.

8. *Ultimate course*

Nine months after the end of the study, ten patients were residents of the hospital. Six of them had remained in the hospital continuously, four had been released but had later returned. Twenty-one patients were living in the community, two of them in foster care. One patient died of a heart condition nearly a year after administration of imipramine.

Four patients were continued on imipramine after the end of the study; three of them left the hospital. One patient received a monoamine oxidase inhibitor. Three patients were treated with electroconvulsive therapy (ECT) and of these one left the hospital. Ten patients were treated with ataractic drugs; of these, two had previously received ECT. Sixteen patients required no specific somatic therapy other than that received in the trial.

OL.
1
62/63

DISCUSSION

Before discussing the results obtained in this study, it may be worth commenting on the doses and route employed, and the duration of treatment. Our initial maximal level of imipramine dosage (400 mg/day) produced toxic symptoms in some patients, so that subsequently the ceiling dose was reduced to 200 mg/day. This appears in keeping with the experience of most investigators. It is possible that by going too high in dosage in some patients, we may have overlooked drug improvement by producing drug toxicity, but such an indictment cannot be levelled at the majority of the patients studied. We have also avoided the use of parenteral medication, since the oral route has been found satisfactory by most investigators. The duration of therapy (4 weeks) while perhaps not sufficiently long to produce benefit in all patients likely to receive aid from imipramine, has been found adequate for most patients both in uncontrolled[2] and controlled [3] trials. No supplementary drugs, such as phenothiazines, were employed, in order to simplify the experimental procedure.

Of considerable importance, perhaps, is the question of the diagnostic categories utilized in this and other studies. Kuhn,[1] in his original paper, stated that imipramine "appears to be most effective in typical endogenous depressions, including those which first occur in the menopause. . . . Depressive symptoms associated with schizoid or schizophrenic features seem to have a somewhat less certain prognosis. . . . It is even more difficult to answer the question whether reactive depressive states respond to [imipramine] therapy". Freyhan,[4] Lehmann *et al.*,[5] Keup *et al.*,[6] Weiss,[7] and Azima[8] seem to have come to similar conclusions. On the other hand, Pollack,[9] while finding schizophrenics essentially unresponsive, had improvement rates in his psychoneurotic and reactive depressions which were as satisfactory as those for the endogenous depressions; and Ruskin and Goldner[10] reported no clear-cut differential response in their various diagnostic categories, with good results even in the schizophrenics.

One ready explanation for such disagreements may lie in the semantics of psychiatric diagnosis. Kielholz and Battegay[11], for example, refer to "depression due to exhaustion,"

a category not easily equated with any used in the present study. FAZIO *et al.*[12] likewise refer to "grave or atypical depressions" classifiable into "delirious melancholia with paranoid disorder, melancholic blocks, puerperal depressive psychoses". Perhaps most indicative of the potential confusion in this field is the report of MANN and MACPHERSON[13], who classify forty patients as "neurotic depressive reactions", but then go on to say that "the vast majority of patients of this diagnosis may be thought of as 'involutional melancholiacs' ".

Our own data, scanty though they be, would seem in keeping with the majority of reports, i.e., the best results with imipramine were seen in endogenous depressions. When our results are examined, it is obvious that significant improvement occurred in at least some patients in *every* diagnostic category during the four weeks' trial on placebo. BALL and KILOH[3], in a larger controlled trial, also found "good response" to placebo in 20–22% of patients, both in "endogenous" and "reactive" depressions. They did, however, find significantly better performance with imipramine in both major groups. Our data show a trend in favor of imipramine in psychotic depressions, but the drug–placebo differences are small enough so that a sample size several times as large as the present one would have been required for convincing statistical differences. In a small, short-term controlled comparison of placebo and imipramine, SLOANE *et al.*[14] were unable to distinguish between the two. Obviously the categorization of certain depressed patients as individuals who would unquestionably "have required electroshock" without other treatment[8] is a risky and uncertain guessing game. More appropriate would seem to be the sentiments of SLOANE *et al.*[14] who said: ". . . we wonder what proportion of patients who are considered these days suitable for ECT at the time of hospital admission would spontaneously improve if merely left alone. We suspect that it may be much higher than is customarily believed". In this light, KARAGULLA's paper[15] is of importance. She found that 80–90% of depressive patients recovered or improved even in the pre-ECT era, and that a relatively large number of patients required only 6 weeks' stay in hospital. In our own group of thirty-two patients, half required no specific somatic therapy other than that received in the experiment.

The question arises as to how much a change in milieu might be responsible for the improvement observed in all of our patients, but especially those under placebo treatment. Any patient leaving his home and being admitted to a mental hospital is of course exposed to a "milieu therapy" of some sort. This, undoubtedly, accounts for the known fact that the discharge rate of depressive patients has always been high during the first three months of hospitalization in a mental hospital even before the advent of ECT or psychopharmacological agents.

Selective influence of the milieu — by transfer from one ward to the other — was avoided in our study. All patients in the study group as well as those not participating in the study were treated alike as to transfers. The ward physician (who was unaware of the medications the study patients were receiving) routinely transferred from the admission ward to an open ward those patients who had shown sufficient improvement.

There are still all too few papers published on psychopharmacologic therapy that give any data other than percentages of patients showing global "improvement", "worsening", or "no change". In defining and communicating degrees of improvement or deterioration in patients, an adequate check list or rating scale is extremely important, although such

VOL. 1 1962/

instruments are obviously dependent on the ability and conscientiousness of the rater. Rating scales are particularly useful in recording and describing change when there is "paradoxical" improvement along one parameter and worsening along another.

In the use of the two types of observers in this study, it is of interest that the ward observers reported more therapeutic benefit to the patients — whether on drug or placebo — than did the physician. This discrepancy might be explained by the fact that patients in a structured interview of short duration might appear apprehensive whereas on the ward they might be relaxed. In addition, probing by an experienced psychiatrist might elicit the presence of depressive features not apparent to the ward personnel. On the other hand, the ward personnel, being in constant contact with the patient, might observe features which are not accessible to the psychiatrist in a short interview. It is thus not difficult to visualize the possibility that different types of observers may arrive at quite different conclusions; it therefore is important that one employ similar observers in the comparison of all treatments under study.

OL.
1
62/63

The double-blind aspect of the present study was effective in disguising the treatments except in those few patients in whom severe side effects occurred from imipramine. One interesting side effect of imipramine is the leucocytosis and eosinophilia occasionally seen with the drug. Kuhn[1], Kielholz and Battegay[11] and Mann and Macpherson[13] have commented on the phenomenon, which may occur without any other evidence of hypersensitivity.

SUMMARY

Imipramine and placebo have been compared in a double-blind controlled trial in the therapy of depression. Significant improvement occurred in all diagnostic categories of depression over a four-week period of placebo administration. Imipramine appeared somewhat more effective (although not statistically significantly so) than placebo in endogenous depressions, but not in neurotic or schizophrenic depressions, although the number of cases in all categories was small.

The use of a cross-over design proved unfeasible because of differential dropouts, but served to demonstrate that "failures" on drug are not necessarily greater therapeutic challenges than previously untreated cases.

The employment of rating scales was found helpful in following individual components of the depression. Ward attendants were more likely to see therapeutic improvement from drug and placebo than was the psychiatrist observer.

Perhaps the most important fact emerging from the data was the favorable short-term prognosis of many of these severely depressed patients. Reports of "percentage improvement" in uncontrolled drug trials in this psychiatric area are likely to be spuriously high and cannot be accepted at face value as evidence for therapeutic efficacy. Furthermore, the placebo success rate appears sufficiently high to require anti-depressant drug trials of considerable size in order to provide convincing evidence of drug differences. In view of the small number of depressed patients available at most institutions, this poses a problem of major magnitude.

APPENDIX I. PHYSICIAN'S RATING SCALE FOR DEPRESSION

	0	1	2	3
Mood				
Facial expression	Average play of facial expression	Sad; smiles sometimes	Sad, with some degree of responsiveness	Immobile expression of sadness
Anxiety (subjective)	Absent	Mild a/o occasionally	Mod. severe a/o mod. frequent	Severe a/o continuous
Hostile attitude	Absent	Passively hostile and resistive to interview	More actively uncooperative, ironic and bitter	Sarcastic, angry a/o belligerent
Crying	Neither wants to nor does so	Cries occasionally	Cries frequently	Wants to but cannot
Subjective mood	No feeling of sadness	Feels sad a/o unhappy		Feels terrible and feels he cannot go on
Psychomotor				
Slowing down of movements	None	A little slowed down	Markedly slowed down	Practically immobile
Overactivity of movements (Handwringing, pacing)	None	At intervals	Most of the time	Continuously
Speech, decrease in productivity	None	Unresponsive	Frequently silent	Mute or largely so
Pathological thinking				
Morbid thought content (regarding past and present sin, failure, guilt, obsessions)	Absent	Present, but not of deep concern	Moderately preoccupied, but not insisting during interview	Painful, greatly preoccupied with fixed ideas
Regarding future (hopelessness)	Absent	,,	,,	,,
Suicidal thoughts	Absent	Occasionally present	,,	,,
Expression of delusions (self-accusatory, persecutory, somatic)	None at time of inquiry	Occasionally present a/o doubtful	,,	,,
Slowing down of speed of thinking (subjectively)	None	Slower than usual	Needs long time to form a clear thought	Unable to think clearly
Somatic				
Ability for productive occupation	Can occupy himself and feels able to do so out of hospital	Can occupy himself in hospital but feels unable to do so outside	Occupied when encouraged	Feels unable to do anything
Fatigue	None	Mild	Mod. severe a/o Mod. frequent	Severe a/o frequent; greatly preoccupied with
G. I. tract	None	,,	,,	,,
Headache	,,	,,	,,	,,
Heart	,,	,,	,,	,,
Other (specify)	,,	,,	,,	,,
Sleep	Normally	Does not sleep much but does not ask for sedation	Sleeps only with sedation	Says he cannot sleep in spite of sedation

VOL. 1 1962

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OL.
1
62/63

THE MULTIPROFESSIONAL INTAKE ASSESSMENT OF OLDER PSYCHIATRIC PATIENTS*

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VOL.
1
1962/

One of the prime prerequisites for the planning of programs for the treatment or rehabilitation of psychiatric problems in the nonhospitalized older person is the careful analysis of the presenting complaints which bring such patients to psychiatric attention. Such presenting complaints are the most obvious and objective units of measurement as they refer to the problems of the patient which make him seek help. Their objective assessment, however, requires standard methods of recording and treatment by the many different professional workers who may be involved in intake assessment procedures.

The purpose of the standard intake interview is the rapid definition of the type and relative severity of the patient's presenting problems. Disposition of the patient is then based on the impressions formulated as a result of this brief initial assessment. While procedures and extent of the initial screening interview may vary from one clinic to another, the professional worker first meeting the patient will usually be a psychiatrist, a psychologist or a social worker. The possibility then exists that differences in professional background and training, particularly with respect to the age related aspects of the patient's complaints, might lead to differential sensitivity to different types of psychiatric problems. Moreover, it is possible that the use of language in describing complaints may vary among professions as well as individuals within each profession. Research directed towards resolving these questions is difficult because it will frequently require interference with clinic or hospital admission procedures. Because of the nature of these difficulties, research designs are appropriate which will require a minimum of staff time, but generate a maximum of information which will permit at least a limited test of the relevant hypotheses.

Weiss *et al.*[1] derived a formal system for the classification of complaints by the examination of the case files of approximately 200 out-patients at Malcolm Bliss Psychiatric Clinic

* This investigation is part of a larger study of mental health problems of older persons at the Malcolm Bliss Psychiatric Clinic, St. Louis, Missouri. It is supported by Research Grant M–1252 from the National Institute of Mental Health, U.S. Public Health Service.

† Dr. Weiss is now at the University of Missouri Medical School, Columbia, Missouri.

who were 45 years of age or older. In contrast to studies such as those by LORR and RUBENSTEIN[2] or by TATOM[3], the investigators were not concerned with classification into a nosological system of psychiatric diagnosis, but rather with the meaningful assignment of verbalized complaints to a system on whose terms agreement could be reached by raters with different professional backgrounds.

Using this classification system, a set of representative complaints was obtained which can be used as a common data language for the description of patient complaint behavior. It should be stressed that this is not an artificially constructed set of terms, but one derived from the actual complaint behavior of the older psychiatric patient. The question remains, however, whether professional persons with different training will be able to use this data language uniformly or will assign special meaning relevant to their own background.

OL.
1
62/63

In an earlier study[9] it was found that when members of the three mental health professions were asked to rank the above-mentioned set of representative psychiatric complaints in order of relative severity, there was more overall divergence among individuals *within* each professional group than among individuals from different professional groups. Can such findings be expected, however, when the actual "live" patient is to be assessed? The present paper is concerned, therefore, with the analysis of an experiment in which three older psychiatric patients were assessed simultaneously by a group of professional raters. Each rater had the identical information, observed the same behavior, and was required to use the same mode and language of behavior description. The analysis of this experiment is concerned both with the overall differences between raters having different professional backgrounds as well as the specific differences in attention given to distinct types of complaint behavior.

METHOD

The complaint classification has been described more extensively elsewhere [1]; it will be summarized here only briefly. Two dimensions were found to be required to place each complaint. These dimensions were called the "determinants" and "referents" of a given complaint. The determinant identifies the specific nature of the complaint, while the referent gives the attributed cause or result to which the nature of the complaint refers. Seven determinants and five referents were found relevant for classification and were named as follows:

Determinants:	Referents:
1. Affective	A. Physical health
2. Anxietal	B. Mental health
3. Behavioral	C. Economic–occupational
4. Mentational	D. Inter-personal
5. Reality distortional	E. Non-situational
6. Social welfare	
7. Somatic	

An example of a complaint which fits in category 1(A) would be: "I am discouraged because I have headaches." The determinant is of an affective nature (i.e., "I am discouraged") and "because I have headaches" indicates a physical health referent. All

complaints could be sorted into one of the thirty-five possible combinations of determinants and referents. A balanced Q-sort sample was composed by selecting two representative complaints from each category, giving a total of seventy complaint units. The Q-sort sample was then used by a panel of professional raters to provide a common language for the assessment of complaints presented by the patients seen in the intake interview sessions.

The panel of professional raters was composed of two psychiatrists, three psychologists and two social workers. All participant raters had the standard qualifications for their respective professions: psychiatrists, M.D. plus eligibility for board certification in psychiatry; psychologists, Ph.D.; and social workers, M.S.W. In addition, all raters had at least five years professional experience. All were engaged in some kind of activity which required contact with psychiatric patients, although the various raters were affiliated with different institutions.

To permit an adequate test of the importance of patient behavior interacting with the rating behavior of the observers, it was decided to select subjects who upon first impression seemed to represent markedly different patient types. Three assessment sessions were held, and the patients screened were a 62-year-old woman subsequently diagnosed as being a paranoid schizophrenic, a 49-year-old male chronic alchoholic with paranoid personality trends, and a 50-year-old woman with symptoms considered to be primarily neurotic. Each of these patients was interviewed by the same psychiatrist-member of the panel for a period of about 30 min, and other panel members were then permitted to ask any question which they felt essential for further clarification. The patient then left the room and each member of the panel ranked the Q-sort sample in order of applicability of the complaints to the patient they had just seen. The patient also gave a self-description of his complaints using the same Q-sort sample.*

VOL.
1
1962/

RESULTS

The design of our experiment lends itself to the examination of a series of hypotheses which may be tested by means of the analysis of variance. The design is a modification of one presented by Edwards[4] and is summarized in Table 1, which indicates that our design leads to the identification of eighteen distinct components of variation operating in the described assessment procedures. The hypotheses to be tested may be conveniently divided into two groups. The first set of hypotheses is concerned with the question whether our proposed data language is capable of permitting professional raters to identify the distinct complaint patterns of different types of patients and whether there will be reasonable agreement among different raters performing such an operation. The applicable hypotheses of greatest interest and our respective findings may be summarized as follows:

Hypothesis 1. Differing degrees of relative importance will be assigned to the complaint

* The use of Q-technique methods permits tests of certain types of propositions even though only few raters and subjects are used[5]. The basic assumption for the present study is that we are dealing with a population of complaints rather than people. Such complaints were collected, assigned to hypothesized dimensions and then ranked by raters. The analysis of variance was then employed to determine whether the hypothesized dimensions do, in fact, exist, and a balanced design was used to test for the effect of certain characteristics of different kinds of raters. When a rater repeats his ratings with different instructions (e.g., assessing different patients), it is also possible to compute correlations among such ratings. The correlations were then factor analyzed specifying a hypothesized factor structure, to see whether the observed data fit certain hypotheses as to the dimensionality of rating behavior.

TABLE 1. SUMMARY OF THE ANALYSIS OF VARIANCE FOR THE Q-SORT RATINGS IN THE MULTIPLE ASSESSMENT PROCEDURE*

Source of variation		Sum of squares	d.f.	Mean square	Error term	*F*-ratio
a	Raters	0	5	0	*	
B	Patients	0	2	0	*	
C	Referents	382·01	4	95·50	aC	20·06‡
D	Determinants	195·13	6	32·52	aD	5·06‡
aB	Raters × Patients	0	10	0	*	
aC	Raters × Referents	95·27	20	4·76	aBC†	1·64
a′C	Professions × Referents	28·61	8	3·58	a′C′	·64
a′C′	Pooled Raters × Referents	66·66	12	5·56		
aD	Raters × Determinants	192·80	30	6·43	aBD†	1·45
a′D	Professions × Determ.	66·54	12	5·54	a′D′	·79
a′D′	Pooled Raters × Determ.	126·26	18	7·01		
BC	Patients × Referents	545·63	8	68·20	aBC	23·44‡
BD	Patients × Determinants	1249·77	12	104·16	aBD	23·46‡
CD	Referents × Determinants	655·53	24	27·31	aCD	15·61‡
aBC	Raters × Pat. × Refer.	116·23	40	2·91	aBCD	1·83
a′BC	Prof. × Pat. × Refer.	60·77	16	3·80	a′BC′	1·64
a′BC′	Pooled Rat. × Pat. × Ref.	55·46	24	2·31		
aBD	Raters × Pat. × Determ.	266·50	60	4·44	aBCD	2·79‡
a′BD	Prof. × Pat. × Determ.	150·36	24	6·26	a′BCD′	1·94
a′BD′	Pooled Rat. × Pat. × Det.	116·14	36	3·23		
aCD	Raters × Refer. × Determ.	210·59	120	1·75	aBCD	1·10
a′CD	Prof. × Ref. × Determ.	117·51	48	2·45	a′CD′	1·90
a′CD′	Pooled Rat. × Ref. × Det.	93·08	72	1·29		
BCD	Patients × Refer. × Determ.	736·93	48	15·35	aBCD	9·65‡
aBCD	Rat. × Pat. × Ref. × Determ.	380·61	240	1·59	e	0·60
a′BCD	Prof. × Pat. × Ref. × Det.	134·21	96	1·40	a′BCD′	0·82
a′BCD′	Pooled Rat. × Pat. × Ref. × Determ.	246·40	144	1·71		
e	Replication	1669·00	630	2·65		
	Total Variance	6696·00	1259			

* For computational simplicity one psychologist was dropped from the variance analysis in order to maintain a balanced design. As a result the analysis represents a mixed model[11] where capital letters indicate the fixed constants and small letters the random variate. Since Q-sorts require forced distributions with equal means and variances, the sums and variances for terms a, B and aB must, of course, be equal by definition.

† No exact tests are available for these terms. The alternate tests used appear to be justified by the following considerations: aBC can be used to test aC since aCD is not significant; aBD can be used to test aD since aCD is not significant.

‡ Significant at or beyond the 1% level of confidence.

categories represented by each of the dimensions of our classification system. *F*-ratios for the overall differences among both referents and determinants, as well as their simple interaction, were found to be significant at or beyond the 1% level of confidence. One may infer, therefore, that our classification system is meaningful to the extent that it permits assigning significantly different importance to the different complaint categories.

Hypothesis 2. Different raters are likely to show significant disagreements in their rating of the same patient: None of the observed differences was large enough to be

significantly greater than chance expectancy and it is concluded that there was good overall agreement among all raters for all complaint dimensions.

Hypothesis 3. Differences in assigning relative importance of the various complaint dimensions may depend upon the type of patient being rated: All the differences with respect to this hypothesis were significant at or beyond the 1% level and it appears that assignment of the importance of specific complaint dimensions and categories depended on the type of patient observed.

Hypothesis 4. Differences in assigning importance to the various complaint dimensions for different patient types may depend upon differences among raters: Our conclusions here are equivocal and suggest that there may be significant differences among raters in assigning different importance to the referents and determinants, depending on the patient type involved, but that such differential assignment does not extend to the individual complaint categories.

The second group of hypotheses is concerned with the question whether differences in professional background will lead to different patterns of symptom identification:

Hypothesis 5. Differences in assigning relative importance to the various complaint dimensions do not depend on the professional background of the raters: None of the respective differences is significant and it may be concluded that differences among individuals within a given professional group are as large or larger than the differences between professional groups.

Hypothesis 6. Differences in assigning importance to the various complaint dimensions for different patient types may depend upon differences in the professional background of the raters: None of the respective differences was found to be significant and it is clear that patterns of complaints identifying different types of patients are equally assigned by members of the different professions.

Since each Q-sort rating yields a set of seventy scores it is possible to compute relatively stable correlations among the Q-sorts from all the raters, and also with the self-descriptions of the patients. Correlations of the self-description of patient A with the professional observations range from 0·49 to 0·63 while correlations among the professional observations of this patient range from 0·64 to 0·84. For patient B the correlation ranges are from 0·29 to 0·42, and from 0·31 to 0·68 respectively; and for patient C from 0·18 to 0·47, and from 0·50 to 0·86 respectively. These correlations suggest that while patients may or may not perceive the relevance of a sample of complaint statements in the same way that skilled professional raters do, the professional raters tend to show substantial agreement among themselves in assessing the patient's complaints.

THE HYPOTHESIS-TESTING FACTOR ANALYSIS

Recent views on factor-analytic procedures suggest that this method may in many instances be of considerable value in testing hypotheses as to the presence or absence of a set of given factors.[6] The experimenter groups those variables which are hypothesized to have significant loadings on a specific factor and then proceeds to test whether this proposed structure can in fact be found. The method used in this paper is a modification of Thurstone's multiple group method[7] and is more fully described in a paper by Horst and Schaie.[8]

VOL.
1
1962/

The pattern of correlations suggests that the magnitude of agreement among professional raters is probably quite independent of specific professional background. To test this latter proposition, a factor-analytic design was used, and a six-factor hypothesis was specified. Factor I was specified as a factor unique to Patient A, Factor II to Patient B, Factor III to Patient C, Factor IV to the unique variation attributable to psychiatric training and background, Factor V to psychological training and background, and Factor VI to the social work background.*

The results of this procedure demonstrated a good fit for the factors identifying the three patients, giving further support for the proposition that raters are well able to use our data language in Q-sort form to describe patterns of complaint behavior unique to each of the patients. Factors IV and V, however, are clearly shown not to exist; i.e., there was no variance which would be attributable to a factor held in common by the psychologists alone or the psychiatrists alone but which had no loadings by members of the other professions represented. Factor VI is equivocal and suggests that there may have been some variance attributable to the social workers. There is overlap, however, in that one of the psychologists and one of the psychiatrists have moderate loadings on this factor also. Perhaps this factor represents a complaint dimension not unique to the social workers' background, but rather one to which their background would tend to sensitize them.

The average factor loadings for all the ratings derived from observers with common professional background is shown in Table 2.† These results suggest, that regardless of

TABLE 2. AVERAGE FACTOR LOADINGS FOR THE THREE PROFESSIONS*

	I	II	III	IV	V	VI
Psychiatrists	0·84*	0·47*	0·57*	0·14	0·11	0·10
Psychologists	0·88*	0·49*	0·65*	0·09	0·15	0·12
Social Workers	0·83*	0·41*	0·65*	0·06	0·08	0·32*

* Factor loadings are considered to be significantly greater than zero if they exceed 0·25.

* Tables listing the correlations among ratings as well as the factor loadings for the multiple-group analysis and its oblique rotation will be found in an appendix deposited with the American Documentation Institute. Order Document No. 6640, from American Documentation Institute, Auxiliary Publications Project, Photoduplication Service, Library of Congress, Washington 25, D.C., remitting in advance $1.25 for 35 mm microfilm or $1.25 for photoprints. Make checks or money orders payable to: Chief, Photoduplication Service, Library of Congress.

† For the interpretation of the findings summarized in this table it was decided to consider factor loadings of 0·25 or greater as being substantial enough to warrant positive interpretation. The authors are not aware of any published discussions of sampling distributions for factor loadings obtained from the multiple-group method. Conventionally a cut-off point for interpretation is based on the size of the sample used. Our correlations are based on a sample of seventy items. If we were to utilize the sampling distribution of the product–moment correlations coefficient, we would find that for a sample of this size a correlation would be significantly greater than zero at the 5% level of confidence if it exceeds a value of 0·24. The preceding considerations led to our admittedly arbitrary decision with respect to the interpretation of the factor loading matrices.

the raters' background, they were most successful in assessing a patient with apparently clear-cut psychotic symptoms, had lesser success with a patient showing neurotic symptoms, and were least successful (although still showing marked agreement) in assessing a patient with mixed symptomatology. Only the social workers had an average loading which exceeds chance expectation on one of the hypothesized professional identification factors.

DISCUSSION

The principal finding of our study was that high agreement occurred among raters with different professional backgrounds in assessing the presenting complaints of older psychiatric patients in a screening interview situation. When semantic confusion is cleared, by requiring the use of common descriptive procedures, such assessment is found to involve an area of overlapping professional skills. In our panel of observers, at least, experience in dealing with patients may have been a more crucial variable than the specific professional affiliation and training of the rater.

In the theoretical sort[9], where raters had been asked to Q-sort items in order of their severity in disabling the patient, social workers showed a tendency towards greater concern with complaints relating to personal welfare, while psychologists and psychiatrists were most sensitive to reality distortions. When dealing with real patients, however, the expected bias of the social workers did not appear. Indeed, they were now the raters most sensitive to reality distortions and least sensitive to behavioral complaints.

It seems important to note that the major factor contributing to the differences among the ratings was found to be a function of the differences among patients interviewed, rather than in differences attributable to characteristics of the raters. Also, the patients' self-description showed the greatest agreement with the assessment provided for them by the professional raters when symptoms were clear-cut and overt, while there was least agreement when symptoms were mixed or obscure.

The results of our present and earlier studies suggest that a common system of complaint classification in assessing the older psychiatric patient can be used in a consistent and reliable manner. While our complaint sample was collected from a group of older patients, preliminary studies would suggest that it is equally applicable for psychiatric patients at all adult age levels. In this context normative studies of complaint behavior involving cross-sectional and longitudinal samples would be desirable and warranted.

In the context of a study of the dynamic patterns of symptom formation in older patients[10] it was noted that the major foci of complaints in order of emphasis were related to physical health, social welfare and last of all psychiatric problems. It seems that some of our patients coming to a psychiatric facility were utilizing an inappropriate referral source. Anyone familiar with patients in medical outpatient clinics or social service agencies will be aware of the incidence of similar misdirection of patient complaints. In view of the success of our procedure and its application by professional raters of different backgrounds it would therefore also seem to offer an appropriate approach for an identification and definition of the most significant areas of difficulty a person seems to experience regardless of the agency to which the complaints were first presented.

VOL.
1
1962/

It may be asked whether our investigation demonstrates no more than the possibility that mental health workers can be trained to use a Q-sort rating procedure with high agreement. In reply it should be pointed out that our raters had no previous experience with the Q-sort used and that their highest agreement was found with respect to the first patient interviewed. The promise of our method lies in the nature of the data language utilized. The complaints involved are the ones which bring the patient to professional attention and as such are readily understood both by the patient, in self-description, and by the professional worker receiving such information. The use of a basic data language which can be used at different levels merely by a manipulation of instructions has proven most fruitful in the area of selfconcept study. An extension of such a model into the area of psychiatric description is offered by means of the operations described in this paper.

OL.
1
62/63

SUMMARY

Two psychiatrists, three psychologists and two social workers participated in a multiple-assessment panel which interviewed three older psychiatric patients with the aim of eliciting their presenting complaints. The panel participants were then asked to rank by means of Q-sort methods, a sample of representative complaint statements derived from the study of the case files of older psychiatric outpatients, in order of their applicability to the patient just observed.

It was found that when the same units of description were used, raters with different professional background did not show any significant differences in their complaint assessment. In fact, there was marked agreement among panel members and the principal differences found were related to the distinct complaint patterns ascribed to different patients. A hypothesis-testing factor analysis was further used to examine the correlations among all ratings. Distinct factors with substantial loadings on every rater, emerged for each of the different patients. Highest agreement was shown when symptoms were clear-cut, but marked agreement prevailed even when symptomatic behavior was mixed and obscure. It was hypothesized that a distinct factor might be found also for each of the professional backgrounds represented in the panel with loadings on all ratings made by members of the respective professional groups. No such factors appeared for the psychiatrists or psychologists and only an equivocal factor emerged for the social workers.

Use of an appropriate common data language leads to the recognition that description of the presenting complaints of psychiatric patients may constitute an area of overlapping skills among the three mental health professions. While further studies might identify other factors (e.g., degree of familiarity with the patient, knowledge of psychopathology, etc.) to be of importance, it seems clear from this study that clinic intake responsibilities might well be assigned without regard to the professional affiliation of the staff member involved.

The present study further provided an example of a methodology which permits the test of a series of hypothesis about the utilization of professional skills with a minimal expenditure of professional time or interference in clinic routine. As such it provides a model for further studies of professional problems as well as illustrating the use of a technique which should prove a valuable tool for the description of psychiatric complaint behavior.

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VOL.
1
1962/

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A COMPARISON OF THE URINARY METABOLITES OF L-HISTIDINE-C^{14} IN SCHIZOPHRENIC AND NORMAL SUBJECTS

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OL.
1
62/63

SEVERAL groups of workers have reported differences in the metabolism of histidine or its derivatives in normal humans and schizophrenics. Most of these studies have been directed towards the physiologically active metabolite, histamine. GOOSZEN and DONKER[1] have reviewed the literature in this field and reported elevated blood levels of histamine in schizophrenic patients. An attempt has been made to relate this finding to both the reported insensitivity of schizophrenics to histamine[2, 3] and the lack of asthma and other allergic disorders in these patients[4]. Skin reaction to histamine[5], and the effect of tranquilizing agents on histamine tolerance and binding[4, 6] have been compared in normal and schizophrenic subjects. In one study[7] the claim was made that histidine excretion was somewhat lower in a group of mental patients than in normals (presumably under comparable dietary conditions).

In view of these findings, analysis of the urinary metabolites of uniformly radioactive L-histidine has been carried out on a group of adult male schizophrenics and a group of normal males, as part of the programme on biological aspects of schizophrenia conducted by this laboratory[8]. Inasmuch as the warranted dose of radioactivity was inadequate to permit the detection and quantification of histamine or its metabolites, the elucidation of histamine metabolism in two such populations will require entirely different techniques.

EXPERIMENTAL METHODS

The selection of patients has been described[9]. Twelve schizophrenics and eleven volunteer control subjects were presented with identical diets for 2 weeks prior to the experiment. All medications including supplementary vitamins were withheld for 3 weeks before the experiment.

The radioactive histidine was administered to four normal control subjects and four schizophrenics on three successive mornings. (On the final morning there were only three control subjects). Food and liquids were withheld from 9.00 p.m. on the evening before

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the experiment until 1 p.m. on the following day to reduce the urine volume. The subjects received 10μc (0·7μc/mg) of uniformly radioactive L-histidine-C^{14} dissolved in a glass of orange juice immediately after voiding at 9.00 a.m. in the morning. Urine was collected for 5 hr (until 2.00 p.m.) in a single container with 5 ml of toluene added as a preservative. After measuring the volume and removing small aliquots for counting, the specimens were frozen.

Processing the urine

When all the urine collections were completed, the subjects were assigned random numbers, the specimens coded by numbers, and processed in numerical order. Because of the high salt content of the specimens and the low radioactivity, it was necessary to concentrate and partially desalt them before fractionation. The technique for this has been described elsewhere[10], and consists essentially of an initial evaporation *in vacuo* followed by an 80% ethanol precipitation, filtration and reconcentration of the filtrate. Because of the possibility that a compound might be preferentially lost during this concentration and desalting procedure, the per cent recovery of radioactivity was measured along with other variables (Table 1). The final residue was dissolved in 10–15 ml of distilled water and aliquots were taken for counting and ion exchange fractionation.

VOL.
1
1962/

Fractionation and separation of histidine-C^{14} metabolites

A two-step ion exchange column fractionation has been developed to separate the metabolites and is described in detail elsewhere[10]. The concentrated radioactive urine was first passed through a Dowex-1-acetate column. The wash water containing the basic metabolites was concentrated and added to a Dowex-50-sodium column. Metabolites adsorbed on the Dowex-1-column have been shown to be eluted with varying concentrations of acetic acid in the following order: first, imidazoleacetic acid, ribosylimidazoleacetic acid, methylimidazoleacetic acid, and urocanic acid are eluted together; then, formiminoglutamic acid and glutamic acid in a single peak followed by hydantoin propionic acid and finally an unknown metabolite[10]. The Dowex-50-sodium columns were eluted with sodium phosphate buffer, pH 6·6, according to the method of TALLAN *et al.*[11] This technique is especially designed to separate the ring-N-methylated histidines from histidine. Histamine is finally eluted from the column with 4*N* HCl. All samples were collected automatically. The Dowex-1 elution required 120 tubes (50 drops/tube); the Dowex-50 separation was accomplished in 115 tubes (60 drops/tube). Aliquots of alternate tubes were counted in a liquid scintillation counter[10] and the radioactive peaks were pooled. The final identification of radioactive metabolites was done by isotope dilution techniques, using the pooled peaks directly[10]. After each metabolite had been assayed in the manner described, it was finally expressed as the per cent of administered radioactivity. After all the assays were completed, the code was broken and the data analyzed statistically.

RESULTS AND DISCUSSION

Table 1 summarizes the findings. Values obtained for substances in the urine of normal subjects did not differ significantly from those of schizophrenics. Furthermore, the detailed

fractionation procedure (Fig. 2)[10] which was performed for each of the twenty-three subjects revealed no new peaks present or normal peaks absent in any of the schizophrenics.

TABLE 1. COMPARISON OF THE RADIOACTIVE URINARY METABOLITES OF L-HISTIDINE-U-C^{14} BETWEEN NORMAL AND SCHIZOPHRENIC SUBJECTS

Variable	Mean	Schizophrenics variance	S.D.	Controls		S.D.	t differences between means
				Mean	Variance		
1. Amount excreted	2·883	0·462	0·68	2·836	0·471	0·69	0·165
2. Percentage excreted C^{14} recovered after concentration procedure	65·067	268·586	16·4	70·791	326·181	18·1	0·797
3. Hydantoin propionic acid	0·058	0·002	0·043	0·087	0·002	0·045	1·606
4. Histidine	0·890	0·223	0·47	0·877	0·229	0·48	0·062
5. Methylhistidine	0·008	0·00006	0·008	0·011	0·0002	0·016	0·654
6. Free and conjugated imidazoleacetic acid	0·337	0·199	0·45	0·261	0·037	0·19	0·519

All values except variable number 2 are expressed as percentages of the injected radioactive dose.

An analysis of the individual values comprising the six variables reported in Table 1 revealed three values which varied more than two standard deviations from the mean, but none which significantly differed at the 1 per cent level. All three were different variables and on different subjects; two were schizophrenics and one was a normal control. Since there were twenty-three patients and six parameters studied, there is a total of 138 values. One would expect seven of these to vary from the mean by two standard deviations (5 per cent). Because of this it is difficult to attach significance to these three aberrant figures.

It is possible that the 35 per cent of excreted radioactivity lost during the concentration procedure might have contained a compound common only to one group. However, the fact that there is no significant difference between the amount of C^{14} unaccounted for in both groups makes this unlikely.

It must be emphasized again that this technique yields no information on the histamine pathway of histidine metabolism, since no radioactive histamine or methylimidazoleacetic acid could be detected in the urine of these subjects during the first five hours after the ingestion of radioactive histidine[10]. Histamine has been reported in human urine[12], but that present at any given time is probably derived from histidine ingested several days earlier. SCHAYER has shown that the radioactive histamine formed from histidine-C^{14} in rats is slowly liberated over a period of days. Injected histamine-C^{14}, on the other hand, is rapidly metabolized and practically all the radioactivity is excreted within 24 hr.

It is difficult, if not impossible, to assess the magnitude of metabolic pathways through measurement of urinary metabolites of most amino acids because of the known diversion of many intermediates to general metabolic reactions in the body. Histidine unlike most other amino acids has several catabolic pathways which ultimately result in the excretion of unique end products, e.g., the metabolites of histamine, the 2-methylated histidines and hydantoin propionic acid. Therefore, it was thought that a quantitative study of the urinary

metabolites of histidine might yield some information regarding the metabolism of this amino acid in schizophrenics, if an abnormality actually did exist in these patients. Since the urinary metabolites of radioactive histidine had not been studied in primates previous to this investigation, human urinary excretion patterns were studied in detail, as reported by BROWN *et al.*[10] Although no differences between schizophrenics and normals were observed in the present study, the following observations pertaining to human metabolism of histidine have been made:

Radioactive urocanic acid could not be detected although this compound has been reported in normal human urine.[15] Hydantoin propionic acid, a newly discovered metabolite of histidine[16], is present in human urine as well as rat and monkey urine. In human urine there is approximately twice as much imidazoleacetic acid in the conjugated form as the free form. Almost all subjects had detectable amounts of free glutamic acid (about 0·01 per cent of the injected dose) and an equally small amount of radioactivity which can be attributed to formiminoglutamic acid. These low levels of radioactivity are just above the limit of detectability by the methods employed here and because of this were not subjected to statistical analysis. An unknown metabolite found in large amounts in both monkey and rat urine is barely detectable in human urine[10].

VOL.
1
1962/

SUMMARY

(1) Uniformly radioactive L-histidine-C^{14} was administered orally to twelve schizophrenics and eleven normal control subjects, and radioactive urinary metabolites were separated and measured.

(2) There was no significant difference between the normal and the schizophrenic groups in the fraction of radioactivity excreted, the amount of C^{14} lost after concentration of the urine, the urinary hydantoin propionic acid-C^{14}, histidine-C^{14}, 1-methylhistidine-C^{14} or the combined value for the free and conjugated radioactive imidazoleacetic acid.

(3) No significant individual variant was found in either group.

(4) No evidence was found for the presence of any qualitatively different radioactive metabolites in the schizophrenic group, nor did any subject in either group lack any of the known major histidine products.

Abstract — Analysis of the urinary metabolites of uniformly radioactive L-histidine was done on a group of adult male schizophrenics and a group of normal males. Uniformly radioactive L-histidine-C^{14} was administered orally to twelve schizophrenics and eleven normal control subjects, and radioactive urinary metabolites were separated by ion-exchange chromatography and measured by isotope dilution techniques. No significant difference was found between the normal and schizophrenic groups in the fraction of radioactivity excreted, the amount of C^{14} lost after concentration of the urine, the urinary hydantoin propionic acid-C^{14}, histidine-C^{14}, and 1-methylhistidine-C^{14} or the combined value for the free and conjugated imidazoleacetic acid-C^{14}. No evidence was found for the presence of any qualitatively different radioactive metabolites in the schizophrenic groups, nor did any subject in either group lack any of the known major histidine products.

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OL.
1
62/63

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PLASMA FREE FATTY ACID CONCENTRATIONS (FFA) IN CHRONIC SCHIZOPHRENIA BEFORE AND AFTER INSULIN STIMULATION

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VOL.
1
1962/

INTRODUCTION

NUMEROUS investigations have suggested various abnormalities of carbohydrate metabolism in schizophrenic patients. A number of authors[1–5] have described a delayed or decreased response of blood glucose to injected insulin in schizophrenic patients. Others have noted decreased oral glucose tolerance,[1, 6] or intravenous glucose tolerance[1, 7] in certain patients. Two studies[4, 5] have described abnormal Exton–Rose glucose tolerance tests in schizophrenic patients resembling diabetic curves after the second glucose load.

In 1942, an anti-insulin effect of the plasma of certain schizophrenic patients was described[8] in which rabbits injected with insulin plus the plasma of schizophrenic patients had a smaller drop in blood glucose than did animals given equal amounts of insulin and normal plasma.

Extracts of urine of schizophrenic subjects injected into rabbits intraperitoneally[9] appeared to cause sustained elevation of blood glucose over a 4-hr period in the majority of animals while such sustained elevation was not observed when the same animals received extracts of normal urine. WALKER and MAYER-GROSS[10] in 1951 confirmed this hyperglycemic factor and associated the potency of the extract with the amount of amino acids in it. MORGAN and PILGRIM in 1952[11] again confirmed the presence of a hyperglycemic factor in schizophrenic urine.

MEDUNA and MCCULLOCK[12] defined a subgrouping of schizophrenia called "oneirophrenia" by certain psychiatric and physiologic criteria. Confusion and clouding of the sensorium clinically separated the patient with "oneirophrenia" from other schizophrenic patients. Moreover, three abnormalities were noted typically within this group: delayed or decreased glucose response to injected insulin, the urinary hyperglycemic factor, and decreased tolerance to oral and intravenous glucose. MAYER-GROSS[5] in 1952 confirmed the presence of these abnormalities in many schizophrenic patients, but could not demonstrate that they were more frequent in any clinical subtype or that they occurred together with more than random frequency.

Other changes have been noted in the carbohydrate metabolism of schizophrenic patients. HENNEMAN *et al.*[13] described abnormal changes in citric acid, α-ketoglutaric acid, inorganic

phosphorus and lactic acid plasma concentrations with oral glucose stimulation. GOTTFRIED *et al.*[14] found abnormal changes in serum citric acid concentration after 20 units of insulin intramuscularly in seven of twelve patients. GOTTLIEB *et al.*[15, 16] measured the specific activity of radioactive phosphorus in both ATP and fructose-1-6-diphosphate after insulin stimulation in schizophrenic and normal patients. Specific activities of both substances rose in normal patients, while that in a number of chronic schizophrenic patients fell. Recently, FROHMAN *et al.*[17] have noted that the incubation of chicken red blood cells with the plasma of schizophrenic patients alters the metabolism of these cells toward an increase in lactate–pyruvate ratio when compared to those ratios obtained by incubating chicken red blood cells with the same amount of normal plasma.

Of interest is the observation that all of these various metabolic abnormalities except the *in vitro* studies have been noted not in the equilibrium state, but rather in response to a specific stimulus — usually either injected insulin or oral glucose.

DOLE[18] and GORDON and CHERKES[19] in 1956 noted a relation between plasma free fatty acid concentrations (FFA) and glucose metabolism. They described a consistent fall of FFA after the injection of glucose or the injection of insulin. BIERMAN *et al.*[20] noted profound FFA rises in patients with uncontrolled diabetes and stressed the belief that plasma FFA concentrations varied inversely with glucose utilization and not apparently with the glucose concentration. They also noted that with the use of radioactively-labelled FFA, insulin affects only the mobilization and not the utilization of FFA.

Because of the previously noted abnormalities of glucose metabolism in schizophrenia and the relationship of plasma FFA concentrations to glucose metabolism, FFA concentrations were measured before and after the intramuscular injection of insulin in normal and schizophrenic subjects.

EXPERIMENTAL SUBJECTS AND FACILITIES

Two series of studies were done involving twelve male chronic schizophrenic subjects without somatic illness and twenty normal male subjects (nonschizophrenic, without "medical" illness). The criteria on which the schizophrenic patients were selected for hospitalization at this facility have been presented elsewhere[21], as have the general characteristics of the population of volunteers from which these normal subjects were selected.[22]

The normal volunteers and schizophrenic patients lived separately on similar patient units. They were fed regular hospital diets *ad libitum*. Coffee and tobacco were unrestricted. The range of physical exercise among individuals in each group varied from very active to sedentary but the normal group were on the average more active. The average daily food intake for the schizophrenic patients was 2900 calories, while that for the normal volunteers was 3500 calories. Average daily carbohydrate consumption was 301 g for the schizophrenic patients and 325 g for the normal subjects.

PROCEDURE AND METHODS

Twelve schizophrenic patients and seven normal volunteers participated in the first study. Venous blood was drawn at 8.30 a.m. after an overnight fast. The subjects then ate a light nonfat breakfast of fruit juice, dry toast and black coffee. This was followed by intramuscular injection of 10 units of regular insulin (U-40, Lilly) at 10.30 a.m. and the drawing

of the postinsulin blood at 11 a.m. This procedure was performed in conjunction with a study by FROHMAN *et al.*[23] and followed their protocol except that in the case of the FFA procedure the author was aware of the identity of the bloods. The analyses, however, were performed by assistants who did not have that information.

For glucose determination, 4 ml of blood were placed in fluoride bottles. These determinations were performed within 24 hr by a modification of the HOFFMAN[24] method.* For determination of FFA, 10 ml of blood were placed in tubes containing three drops of heparin (100 mg/cm^3); the tubes were inverted several times and placed immediately in ice.

Plasma FFA were determined by extraction of 1 ml of plasma for 24 hr in a mixture of 2,2,4-trimethylpentane (*iso*-octane) glacial acetic acid, and acetic anhydride, followed by titration against 0·02 *N* NaOH after two washings[25].

The second study involved the same twelve schizophrenic patients but thirteen different normal volunteers who had recently been admitted to the hospital. In the second study, the preinsulin blood was drawn at 8.30 a.m. after an overnight fast and immediately 10 units of regular insulin were injected intramuscularly. At 9 a.m. the postinsulin blood was drawn. Blood glucose and plasma FFA were measured as before.

No insulin reactions were noted during the study except for a moderately increased feeling of hunger in a few normal subjects during the second study and slight weakness in the one normal subject whose postinsulin glucose was 15 mg%.

Finally, the procedure of the second study was repeated on another day with respect to the schizophrenic patients, except that an equal amount of saline was substituted for the insulin injection.

VOL.
1
1962/

RESULTS

First study

The results of the first study are recorded in Table 1. There are no significant differences in blood glucose between the two groups. Each subject had a fall in blood glucose following insulin, and the mean of each group fell significantly ($p < 0{\cdot}01$).

The mean FFA of the normal patients before insulin was 0·41 m-eq./l. which was identical to that of the schizophrenic patients. The FFA response to insulin of a majority of schizophrenic patients was different from the normal response in a number of ways. The group of normal patients had a significant fall in FFA after insulin ($p < 0{\cdot}01$) while the schizophrenic patients, as a group, did not have a significant decrease ($p > 0{\cdot}1$). Whereas all of the normal patients had falls in FFA after insulin, three of the schizophrenics had no change or a rise in FFA (S-3, S-7 and S-9). The normal FFA range after insulin was 0·19 to 0·27 m-eq./l. but eight (S-3, S-4, S-5, S-7, S-9, S-10, S-11 and S-12) of the twelve schizophrenic patients had FFA above the highest normal FFA after insulin.

Second study

The results of the second study are recorded in Table 2. They are comparable to the results in the first study with a few exceptions. The mean blood glucose before insulin of

* The author is indebted to the Clinical Chemistry Service of the Clinical Center NIH for the glucose determinations.

TABLE 1.

Schizophrenic patients	Blood glucose			Plasma FFA		Δ FFA
No.	before insulin	after insulin	ΔG	before insulin	after insulin	after insulin
S-13	—	—	—	0·26	0·16	−0·10
S-4	94	91	− 3	0·45	0·35	−0·10
S-11	—	—	—	0·57	0·49	−0·08
S-9	101	61	−40	0·25	0·28	+0·03
S-5	92	26	−66	0·48	0·30	−0·18
S-1	92	52	−40	0·37	0·27	−0·10
S-7	91	39	−52	0·31	0·31	0
S-12	104	72	−32	0·32	0·30	−0·02
S-3	114	88	−26	0·43	0·66	+0·23
S-6	89	64	−25	0·67	0·23	−0·44
S-10	99	72	−27	0·34	0·29	−0·05
S-2	91	78	−13	0·44	0·27	−0·17
	$\bar{X}$ = 96·7 S.D. = 7·8	$\bar{X}$ = 64·3 S.D. = 20·6	$\bar{X}$ = −32·4 S.D. = 18·2	$\bar{X}$ = 0·41 S.D. = 0·13	$\bar{X}$ = 0·33 S.D. = 0·13	$\bar{X}$ = − 0·08 S.D. = 0·16
Normal Patients No.						
N-15	96	84	−12	0·43	0·26	−0·17
N-16	85	58	−27	0·31	0·27	−0·12
N-17	89	68	−23	0·38	0·26	−0·12
N-18	86	61	−25	0·62	0·24	−0·38
N-19	77	52	−25	0·34	0·25	−0·09
N-20	100	90	−10	0·32	0·19	−0·13
N-21	95	58	−37	0·37	0·21	−0·16
	$\bar{X}$ = 89·7 S.D. = 7·9	$\bar{X}$ = 67·3 S.D. = 14·4	$\bar{X}$ = −22·7 S.D. = 9·2	$\bar{X}$ = 0·41 S.D. = 0·10	$\bar{X}$ = 0·24 S.D. = 0·03	$\bar{X}$ = −0·17 S.D. = 0·10
t ratio (Schizophrenic vs. Normal)	1·8	0·3	1·3	—	1·7	1·4

A table of the plasma FFA concentrations, blood glucose concentrations, and their changes after insulin from the first study. Blood glucose in mg% and plasma FFA in m-eq./l. Means, standard deviations and *t* ratio of schizophrenic vs. normal patient means are given for each set of determinations. (ΔG = change in blood glucose and Δ FFA = change in plasma FFA).

the schizophrenic patients is significantly ($p<0·01$) higher than the normal mean. After insulin the means are not significantly different ($p>0·1$).

The means of FFA prior to insulin are identical (0·40 m-eq./l.) for normal and schizophrenic patients as in the first study and are very close to those of the previous study (0·41 m-eq./l.). Normal and schizophrenic patients showed differences in FFA response to insulin which were similar to the first study. The schizophrenic group again had no significant decrease after insulin ($p>0·1$) while the normal group did ($p<0·001$). The mean postinsulin FFA of the schizophrenic patients is significantly higher ($p<0·001$) than

TABLE 2.

Schizophrenic patients	Blood glucose			Plasma FFA		Δ FFA	
No.	before insulin	after insulin	Δ G	before insulin	after insulin	after insulin	after saline
S-13	88	28	−60	0·32	0·25	−0·07	−0·01
S-4	98	96	− 2	0·44	0·41	−0·03	+0·11
S-11	100	81	−19	0·32	0·42	+0·10	+0·02
S-9	94	65	−29	0·39	0·27	−0·12	−0·04
S-5	92	69	−23	0·39	0·42	+0·03	+0·14
S-1	92	38	−54	0·56	0·30	−0·26	+0·01
S-7	92	56	−36	0·46	0·30	−0·16	+0·05
S-12	103	80	−23	0·29	0·30	+0·01	−0·03
S-3	101	86	−15	0·42	0·47	+0·05	+0·06
S-6	95	66	−29	0·36	0·31	−0·05	+0·07
S-10	115	109	− 6	0·44	0·40	−0·04	−0·09
S-2	103	92	−11	0·37	0·24	−0·13	+0·02
	$\bar{X}$=97·8 S.D.=7·3	$\bar{X}$=72·2 S.D.=23·6	$\bar{X}$= −25·6 S.D.=17·7	$\bar{X}$=0·40 S.D.=0·07	$\bar{X}$=0·34 S.D.=0·08	$\bar{X}$= −0·06 S.D.=0·10	$\bar{X}$= +0·03 S.D.=0·07
Normal Patients No.							
N-22	92	62	−30	0·36	0·25	−0·11	
N-23	78	62	−18	0·41	0·25	−0·16	
N-24	86	70	−16	0·44	0·24	−0·20	
N-25	100	90	−10	0·59	0·29	−0·30	
N-26	96	52	−44	0·39	0·24	−0·15	
N-27	94	65	−29	0·24	0·22	−0·02	
N-28	84	36	−48	0·53	0·24	−0·29	
N-29	86	39	−47	0·38	0·29	−0·09	
N-30	81	63	−18	0·57	0·33	−0·24	
N-31	85	15	−70	0·31	0·19	−0·12	
N-32	90	74	−16	0·26	0·18	−0·08	
N-33	97	64	−33	0·34	0·22	−0·12	
N-34	86	61	−25	0·34	0·26	−0·08	
	$\bar{X}$=88·8 S.D.=6·6	$\bar{X}$=57·8 S.D.=18·9	$\bar{X}$= −31·1 S.D.=17·1	$\bar{X}$=0·40 S.D.=0·11	$\bar{X}$=0·25 S.D.=0·04	$\bar{X}$= −0·15 S.D.=0·08	
t ratio (Schizophrenic vs. Normal)	3·2†	1·7	0·8	—	3·9‡	2·4*	

A table of the plasma FFA concentrations, blood glucose concentrations, and their changes after insulin from the second study. Blood glucose in mg% and plasma FFA in m-eq./l. Means, standard deviations, and *t* ratio of schizophrenic vs. normal patient means are given for each set of determinations (Δ G = change in blood glucose, Δ FFA = change in plasma FFA, * = $p<0·05$, † = $p<0·01$, and ‡ = $p<0·001$).

the mean postinsulin FFA of the normal patients. This difference in postinsulin FFA means was not noted in the first study. All of the normal patients had decreases in FFA to a very narrow range (0·18 to 0·33 m-eq./l.) as in the first study. Four schizophrenic patients

VOL. 1 1962/

(S-3, S-5, S-11 and S-12) had rises in FFA and five had postinsulin FFA concentrations above 0·33 m-eq./l. (S-3, S-4, S-5, S-10 and S-11).

Among the schizophrenic patients there is a high correlation ($r = 0{\cdot}76$ and $p < 0{\cdot}01$) of postinsulin FFA in the first and second studies. All of those schizophrenic patients who were abnormal in FFA response to insulin in Study 2 (had either a rise or no fall in FFA, or postinsulin FFA above the highest normal postinsulin FFA) were abnormal by the same criteria in the first study. Two schizophrenic patients (S-7 and S-9) were abnormal in the first study but not in the second study.

Changes in FFA after saline (Table 2) are very small with a range between +0·14 to −0·09 m-eq./l. There is no significant correlation ($r = 0{\cdot}21$ and $p > 0{\cdot}1$) between the change in FFA after saline and after insulin in Study 2.

DISCUSSION

The finding of no significant FFA difference between schizophrenic and normal patients in the "equilibrium state" is in keeping with data regarding other blood constituents such as fasting glucose[3], citrate[13, 14] and lactate[13] which show no significant deviation from normal in schizophrenia except with stimulation (i.e., with insulin, glucose, or epinephrine). Significant elevation of fasting blood glucose in the schizophrenic group was noted in the second but not in the first experiment.

Insulin stimulation did reveal abnormality of FFA response in a number of the schizophrenic patients in both studies. The predictions of FROHMAN *et al.*[23] agree well with FFA

TABLE 3.

Patient No.	Schizophrenia type	Family history	Years hospitalized	Frohman *et al.* (first study)	First FFA study	Second FFA study
S-13	Paranoid	Negative	11	?	0	0
S-4	Paranoid	Positive	10	Yes	+	+
S-11	Catatonic	Positive	12	Yes	+	+
S-9	Chronic undifferentiated	Negative	6	?	+	0
S-5	Paranoid	Negative	16	?	+	+
S-1	Chronic undifferentiated	Negative	5	No	0	0
S-7	Catatonic	Positive	15	Yes	+	0
S-12	Simple	Negative	18	?	+	+
S-3	Chronic undifferentiated	Positive	12	Yes	+	+
S-6	Chronic undifferentiated	Positive	8	?	0	0
S-10	Paranoid	Negative	11	?	+	+
S-2	Paranoid	Negative	5	Yes	0	0

A table showing the schizophrenic patients' number[36], schizophrenia subtype, absence or presence of schizophrenia in their family history, years of hospitalization to date of experiment, the diagnostic predictions of FROHMAN *et al.*[23] from their data obtained during the first study, and results of the first and second studies. (Yes = judged as schizophrenic; No = judged as nonschizophrenic; ? = no commitment made; + = no fall in FFA after insulin or the postinsulin FFA above the highest normal postinsulin FFA: 0 = a fall in FFA after insulin to within the normal range).

criteria of abnormality in Study 1 except for the larger number of patients abnormal by FFA criteria and patient S-2 (Table 3). Those authors were restricted by a "double-blind" protocol, whereas the present study was not "double-blind", but rather viewed in retrospect. The purpose of presenting their predictions is to compare two abnormalities of intermediary metabolism in the same group of patients. It is interesting to note that patient, S-1, the only patient judged "nonschizophrenic" by the psychiatric criteria of FROHMAN *et al.*[23] and, therefore, not included in their report, was normal on both occasions in FFA response.

FFA abnormalities were not restricted to any clinical subtype of schizophrenia, nor is the greater prevalence of FFA abnormalities in patients with family history of schizophrenia statistically significant in this small group. The one correlation which is significant is that of years hospitalized and ΔFFA in the second study ($r = 0{\cdot}57$ and $p<0{\cdot}05$) but not the first study ($r = -0{\cdot}24$). There is no correlation of patient age with FFA after insulin or with ΔFFA.

The cause of this decreased sensitivity of FFA to insulin is not known at present. Increased circulating epinephrine or increased sympathetic activity has been proposed as the cause of a number of the carbohydrate abnormalities which have been reported in schizophrenia[7, 14]. SHAFRIR *et al.*[26] noted in dogs that quantities of injected epinephrine, large enough to abolish the hypoglycemic response to insulin, did not completely abolish the concomitant fall in FFA. No similar data are available regarding norepinephrine. By contrast, those schizophrenic patients who had a rise or no fall in FFA with insulin had significant decreases in glucose concentration. Only two patients (patient, S-4, in both studies and patient, S-10, in the second study) had relatively small decreases in glucose which correspond to the small decrease in FFA. One would expect either abnormally high preinsulin FFA concentrations or significant rises in FFA after saline injection if these patients were secreting amounts of epinephrine or norepinephrine large enough to alter FFA sensivity to insulin. Changes in FFA after saline were not studied in the normal group because of the large amount of data already in the literature[19, 27] which show the average normal rate of increase in FFA due to fasting in the morning hours to be 0·03 in m-eq./l. in 30 min. This is exactly the mean change noted in our group of schizophrenic patients. CARDON and GORDON[27] noted an average FFA increase of 0·084 m-eq./l. in 15 min, during saline infusions in normal volunteers. This would be the equivalent of 0·168 m-eq./l. in 30 min which is higher than the greatest increase after saline injection in our group of schizophrenic patients. In the light of these data, it would seem that schizophrenic patients do not react in excess of normal to the stress of this experimental situation.

Ganglionic blockade and peripheral adrenergic blockade have been shown by HAVEL and GOLDFIEN[28] to decrease FFA response to insulin. Various investigations have suggested impairment in "autonomic responsivity" in schizophrenia[29, 30]. However, HAVEL and GOLDFIEN[28] noted in their dogs a significant fall in FFA upon administering these sympathetic blocking agents before administering the insulin. When insulin was injected, the FFA was already at the concentration to which insulin usually lowered FFA, and no response or only a slight fall was then noted. This is not the case in the group of schizophrenic patients studied here. Prior to insulin their FFA was normal which suggests that no adrenergic blockade was present at that time. It is conceivable that the decrease of plasma FFA with insulin and the resultant increased glucose utilization is mediated through decreased

VOL.
1
1962/

sympathetic nervous system activity *per se*, and that sympathetic regulation is defective in certain schizophrenic patients. This direct role of the sympathetic nervous system in the phenomena which follow insulin injection has not been demonstrated at this time.

The possibility of a plasma insulinase or insulin antagonist[31, 32] might be raised by previous studies on carbohydrate metabolism in schizophrenia. Such a factor could conceivably explain the decreased glucose tolerance, the decreased glucose response to injected insulin, and the urinary hyperglycemic factor noted in approximately 60 per cent of the schizophrenic patients studied by at least one group. An anti-insulin factor might also explain a decreased response of FFA to insulin except for the fact that sizeable falls in glucose concentration were noted after insulin in most of the patients with abnormal FFA responses. The situation of rising FFA in the face of presumably increased glucose utilization is unexplained and especially interesting. It has not been observed in other investigations to this date.

OL.
1
62/63

There were a number of differences between the population of normal patients and schizophrenic patients which may conceivably have contributed to the differences in FFA response. The schizophrenic patients were on the average 16·5 pounds heavier and 13 years older. They chronically consumed more tobacco and coffee. The schizophrenic patients as a group exercised less than the normal volunteers. There appears to be no correlation between FFA abnormality and age in the group of schizophrenic patients. Four of the six patients who were abnormal as to FFA response to insulin were non-smokers and drank little coffee. Three of the six exercised at least a normal amount. Any possible effect of relative obesity cannot be ruled out with certainty in this study, but no similar effect has been reported to date.

The significantly higher fasting blood glucose in the schizophrenic patient group during the second study remains unexplained. Similar difference of means was noted in the first study but was less significant ($p>0{\cdot}05$), possibly because of the higher standard deviation within the groups. A partial explanation may relate to the difference in age between the two groups. The schizophrenic patient age range was between 29 and 42 years, while the normal patient age range was between 18 and 25 years. Hlad *et al.* in 1956[33] reported fasting blood glucose concentrations on a large group of non-diabetic patients of various ages. Fifty-six of these patients were between the ages of 29 to 42 years and twenty patients were between 22 and 26 years. The mean fasting blood glucose concentrations of these two groups were 87·8 mg% and 84·4 mg%, respectively. The older group is significantly higher ($p<0{\cdot}05$) by the one-tailed *t*-test.

Another factor may be related to anxiety or excitement during the study. Blood glucose could have been selectively elevated in the schizophrenic patient group by increased release of endogenous epinephrine or norepinephrine under the stress of the experimental procedure. As noted above, the preinsulin plasma FFA was not higher in this group. The possibility remains, however, that in the schizophrenic patients FFA might not be as responsive as glucose to catacholamines. This would reflect a very real abnormality in schizophrenia because in the normal subject epinephrine and norepinephrine have a more profound effect on FFA than on blood glucose.

Another contributing factor to this difference in fasting blood glucose might be the difference in exercise between the two groups. Exercise has been noted to affect glucose

tolerance[34, 35]. However, as was true with FFA's, there appears to be no positive correlation between exercise and fasting blood glucose within this schizophrenic patient group.

Paradoxical or decreased responsivity of FFA to insulin in schizophrenia remains unexplained. It occurs in approximately 60 per cent of this group of patients, which is roughly the same prevalence reported by others of various abnormalities in carbohydrate metabolism among samples of schizophrenics. Further investigation into response to other factors known to affect FFA mobilization may prove helpful in defining the meaning of these data.

SUMMARY

Twelve chronic schizophrenic patients are compared to seven normal volunteers in the first study and to thirteen normal volunteers in a similar second study with respect to plasma free fatty acid concentrations (FFA) and blood glucose concentrations both before and after 10 units of insulin intramuscularly. Both studies were performed after an overnight fast. In both studies preinsulin FFA means of the normal and schizophrenic patients were identical. Mean fasting blood glucose concentrations were significantly higher in the schizophrenic group in the second experiment. No other significant difference was noted in blood glucose. Both groups of subjects had decreases in blood glucose of similar proportion. In both studies all normal subjects had falls in FFA to a very narrow range. Three patients in the first study and four patients in the second study had rises or no decreases in FFA after insulin. Eight schizophrenic patients in the first study and five in the second study had postinsulin FFA concentrations above the highest normal postinsulin FFA. Correlations are made which show a fair degree of consistency between the two studies.

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VOL. 1 1962/

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PROBLEMS OF SAMPLING AND DIAGNOSIS IN THE MAJOR TWIN STUDIES OF SCHIZOPHRENIA

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VOL.
1
1962

IN ANOTHER paper, I have indicated the advantages of twin studies over other kinds of family studies dealing with heredity in schizophrenia[1]. These advantages mainly involve the definition, ascertainability, and criteria for determining the representativeness of a given sample. The most common objections to twin studies have been:

(1) Twins have almost always been reared together and this common rearing may have contributed to increased concordance in monozygotic (MZ) twins because of psychological characteristics unique to such pairs[2, 3];

(2) Monozygotic fetal twins often share a common maternal circulation, which may disadvantage one as compared to the other, and which may therefore lead to increased *dis*cordance in these subjects with respect to various aspects of the illness[4];

(3) Monozygotic twins have identical genotypes, making it impossible to separate out effects due to an hypothesized primary gene and those due to auxiliary genes in any given pair[5];

(4) Twins are usually born prematurely, and therefore constitute a deviant sample.

The disadvantages are of less importance than the advantages:

(1) Environmentalist concepts implicit in the objection to a common rearing of MZ twins may be tested in various ways[6] and may in fact become refined and improved or disproved in the process;

(2) Factors which make for higher *dis*cordance in MZ twins are of special theoretical interest and may well contribute to a fuller understanding of the etiology of schizophrenia; moreover, since the reported concordance rates in MZ twins hover for the most part about 67 per cent., a high figure indeed as compared to the incidence of the disorder in the population (generally estimated to be about one per cent), the total influence of such factors need not yet concern us unduly;

(3) The need to separate out the effects of postulated primary mutant genes and of auxiliary genes seems premature at this stage of our knowledge, especially when we have still to struggle with the problems of sampling mentioned above, and related ones which I shall explore in this paper. Moreover, although genotypes are identical for any given pair of MZ twins, their variation among a representative sample of such twins should be comparable to the variation of genotypes in any representative sample of schizophrenic subjects, and theoretically at least can therefore be evaluated;

(4) If one objects to a sample of twins on the grounds that there is a high incidence of premature births among them, the objection must be based on the possibility that

prematurity of birth is an added factor causing schizophrenia in these subjects. On the basis of such an assumption, we should expect to find a higher frequency of this disorder in twins. Actually, the best evidence available indicates that no such increase among twins occurs[6], and we may therefore discount the seriousness of this objection.

The task confronting the investigator in twin studies of schizophrenia is formidable, especially when one considers the total number of cases which must be ascertained before a statistically analyzable twin sample of sufficient size can be collected. In the study with the smallest twin sample, approximately 10,000 cases were evaluated to yield a sample of seven MZ twin index cases* said to be schizophrenic[7]. We must therefore acknowledge a considerable debt to the investigators who have carried out such studies: LUXENBURGER[8]; ROSANOFF *et al.*[9]; ESSEN-MÖLLER[7]; KALLMANN[10]; and SLATER[11].

In this paper, I shall examine some of the methodological problems which have confronted the investigators, indicate how they resolved these problems, and clarify the issues surrounding these resolutions so that any future investigators may profit more fully from the work of their predecessors. I shall focus primarily on problems of sampling and diagnosis because I believe that these are the most important ways in which results can be affected so as to lead to erroneous conclusions. Some of the problems and their resolutions will have relevance not only for twin studies or other family investigations of the genetics of schizophrenia, but for all research on this disorder, statistical or experimental.

PROBLEMS OF SAMPLING

The investigator in this field typically starts out by looking for twins with psychopathology of sufficient degree to warrant institutionalization. He does not look just for "schizophrenic" twins, and for the most part he looks only in hospitals or clinics which admit inpatients. Rosanoff *et al.* extended the loci of their search to institutions for the feebleminded, penal institutions, schools and child guidance clinics. KALLMANN also obtained some index cases from institutions other than mental hospitals.†

In none of the studies were cases obtained from psychiatric outpatient clinics, which have not existed in large numbers until relatively recent times, or from the population at large. It is difficult to estimate just what proportion of the total population of persons diagnosable as schizophrenic is thereby missed, but some relevant data are available. Of 3,413 new admissions to the Henry Phipps Psychiatric Outpatient Clinic during a three-year period, 44·2 per cent were diagnosed as having a psychosis (the great majority of these called schizophrenic), but only 20 per cent of all new cases were hospitalized[12]. If these figures are representative, half or more of all diagnosable psychotics may never reach the hospitals from which the major twin samples have been obtained. GAW *et al.*[13], following Bleuler's diagnostic criteria, found that over 52 per cent of the outpatients at their clinic

* Determination of single or multiple birth was made, however, for various reasons, for only 8,586 cases, among whom 179 were found to be twins, eighty-five of unlike sex, and twenty-three of like sex but with a cotwin who had died before adulthood. Among the sixty-nine remaining index twins (two pairs were omitted for special reasons), seven were said to be MZ and schizophrenic, and another four MZ index twins were said to have a disorder which was "related" to schizophrenia. This series of cases will be discussed later.

† KALLMANN, however, made "admission to a mental hospital . . . a definite criterion" for the classification of a psychosis among his index cases.[10]

could be classified as schizophrenic. In a comprehensive community study, SROLE and LANGNER[14] found that 36 per cent of all non-paranoid schizophrenics and 14 per cent of all paranoid schizophrenics resident in a given geographical area were outpatients rather than hospitalized cases. Among 1,660 persons interviewed, tested and rated by two psychiatrists, 24 per cent were said to be "markedly impaired" with respect to social capacity, and among these, 2·5 per cent were hospitalized, 5 per cent were outpatients, 20 per cent were former patients, and 72·5 per cent had never been patients at all. MONROE[15], reviewing the histories of sixty-nine patients whom he had treated for at least 30 hr in 10 years of private practice, stated that although none had been hospitalized, and although it was predicted that none would need hospitalization in the future, 39, or 58 per cent, were ultimately diagnosed by him as schizophrenic. PENROSE[16], in a study of mental illness in the relatives of 1,000 patients, found one uncertified psychotic relative for every 1·74 psychotic relatives who had been certified. Thus, a large number of schizophrenics may never be hospitalized.

Investigators sampling the domain "schizophrenia" must face the problem of whether the inclusion of diagnosable-but-not-admitted psychotics is necessary for their inquiry. The decision depends on the kind of conclusion the investigator would like to be able to draw. If he is willing to restrict his conclusions to hospitalized cases, he has no serious problem. But if he wishes to generalize to the broad population of persons called schizophrenic, he must have the entire range of such cases represented in his sample. With respect to twin studies of schizophrenia, it has been shown[17] that the concordance rate for schizophrenia in MZ twins is much higher when the severity of illness in the index case is relatively great (approximately 100 per cent) than when the illness is mild (approximately 26 per cent). Both figures are based on hospitalized index cases. If we assume that the large majority of diagnosable-but-not-admitted schizophrenics are even less severely ill, then we might well find that the MZ twin concordance rate in such a sample would also be about 26 per cent or less. If these cases were made part of a study which also included hospitalized cases, the overall concordance rate would probably be reduced considerably below the rates previously reported. In any event, such a study would be of interest.

The five investigators have in the main used two procedures to obtain a sample of twins with psychopathology. In the first method, a series of consecutive admissions over a period of years constituted the starting sample. This method was used by Essen-Möller and by Luxenburger. In the second method, which was used by the other three investigators, all patients resident in a number of cooperating hospitals comprised the population from which the first sample of twins was obtained. In the case of the largest study (Kallmann) the total resident population of the cooperating hospitals comprised over 73,000 patients. If we estimate that about one in forty of these cases was a twin, the total yield of twins in this resident population would have been about 1,825, a sizeable number.* The kind of sampling source used makes a difference with respect to the picture of concordance obtained. If one samples from resident populations, concordance with respect to the severity of the

* KALLMANN reports 1,232 psychotic twin index cases in the total sample at the time he compiled his 1950 article[21], suggesting that a large number of twins were not reported. It is highly probable that a large majority of his index cases were obtained from the resident population since the number of new admissions was only one-sixth the number of resident patients.

VOL. 1 1962

schizophrenic illness tends to be high; but if one samples from consecutive admissions, concordance with respect to severity of the illness appears to be much lower[17].

Once the investigator has decided on his source of cases, he must find out which of the cases is a twin. Luxenburger and Essen-Möller had recourse to birth records for such a determination, and therefore were able to minimize any possibilities of systematic error. The remaining three investigators were not so fortunate and had to obtain information about twinship from other sources. In the main, they had to rely on hospital records (which are often reputed to have only fragmentary biographical information), or on the diligence of hospital personnel who inquired of patients and their relatives whether the patient was born a twin or not. Kallmann and Slater each made a great effort to systematize reporting procedures to keep errors and biasing factors low, but it is difficult to render a quantitative estimate of their degree of success in this regard. In many public hospitals, there is a high rate of turnover and a low level of scientific curiosity, training and assiduity among non-professional hospital personnel, and such factors could lead to a certain amount of error. On the basis of LUXENBURGER's study of these matters[8], one would expect that errors which might have occured in this respect would have been in the direction of reporting more MZ twins, and more concordant pairs among both MZ and DZ twins.

OL.
1
62/63

The twins so obtained are called index cases (also, probands or propositi). If both of a pair of twins are found in the sample, both are called index cases. Each index case represents a pair when the Weinberg proband method is applied to twins. To calculate the concordance rate, the formula recommended by ALLEN[18] is

$$\frac{C}{C+2D} = \text{twin concordance rate},$$

where C equals the number of index cases from concordant pairs and D equals the number of index cases from discordant pairs. It is important that investigators have clearly defined criteria as to what constitutes an index case since the numerator in the above formula can be misleadingly high or low if the criteria are too broad or too narrow.

TABLE 1. PROPORTION OF ALL CONCORDANT MZ AND DZ PAIRS IN WHICH BOTH TWINS ARE INDEX CASES

Study	Number of pairs with both twins index cases	Number of pairs with one twin the index case	Total: *Actual* Concordant Pairs	Total: *Index* Concordant Pairs
Luxenburger (1928)*	3	11	14	17
Essen-Möller	0	5	5	5
Rosanoff *et al.*	No information given			
Slater	7	27	34	41
Kallmann (1946)	103	70	173	276

* Includes cases called "probably schizophrenic".

We may examine the consistency of criteria used in the five major studies by noting in each study the number of concordant pairs with both twins called index cases and the number of concordant pairs with only one twin called an index case, comparing the studies in these respects. The relevant data have been compiled and arranged as in Table 1.

It can be seen in Table 1 that in three of the four studies which reported the relevant information, there were about four concordant pairs with one twin the index case for every concordant pair with both twins called index cases. But in Kallmann's series there were actually more pairs with both twins index cases than there were pairs with only one twin the index case. A test of the difference between Kallmann's series and those of the other investigators combined (which are in good agreement on this point) yields a chi-square of 25·24, which is significant at well beyond the 0·001 level, indicating a marked difference in this respect. In Kallmann's series, the ratio of pairs with one twin the index case as compared to pairs with both twins called index cases is 0·68:1, whereas in the other series combined the ratio is 4·30:1, a ratio about six times as large.

It is possible that some aspect of the sampling procedures used could account for this difference between Kallmann and the other investigators. For example, if there were less emigration from the area covered by Kallmann's study than from the areas covered by the other investigators, more *pairs* of twins could have turned up in the sample. However, it seems unlikely that emigration from New York State was *less* than emigration from Bavaria, southern Sweden or London County.

Another possibility may be that the time span covered by Kallmann's investigation was considerably longer than that covered by the other investigators, thereby affording greater opportunity for cotwins to come into the sample as index cases. At the time of his 1946 paper, Kallmann's series had covered a span of nine years. However, Slater began his series in 1935, had his work interrupted during the war, and completed collecting his material during 1947–49, thus spanning a fourteen-year period. On the basis of time alone, the proportion of concordant pairs with both twins index cases should have been *higher* in Slater's series.

A third possibility may be that Kallmann's sample was more completely ascertained than were the other samples. However, I have not been able to find any evidence to support such a position. Procedures such as those used by Luxenburger and Essen-Möller assure a high degree of completeness with respect to ascertainment since they systematically account for all admissions during the time period covered by the sampling.

Fourthly, the possibility exists that there were actually more pairs with both twins hospitalized in Kallmann's sample than in the other samples. We might expect *prima facie* that the frequency of such pairs would be higher in a sample obtained from a resident population than in one obtained from consecutive admissions. However, since the sampling procedures used by Kallmann and Slater were very much alike, and since both sampled from large resident populations, the proportion of pairs with both twins hospitalized should have been similar in these studies.

Dr. Kallmann has graciously provided me with some unpublished tables which enable us to check this point. Among 120 concordant pairs in his 1946/1949 survey of cases, 100 cotwins of the initial MZ index cases had been in a mental hospital at some time. I have checked through Slater's case histories and found that among twenty-four concordant

VOL.
1
1962/

MZ pairs, twenty-one cotwins had been in a mental hospital at some time. The proportions of MZ cotwins with a history of hospitalization for psychiatric disorder were 87·5 per cent in Slater's series and 83·3 per cent in Kallmann's series, indicating close agreement on this point. Therefore, differences between the studies with respect to the frequency of pairs with both twins index cases cannot be explained on this basis either.

If we then exclude these four possibilities, I can think of no others and can only suggest that Kallmann's criteria of what should be called an index case do not coincide with those used by the other investigators. It may be that Slater limited "index cases" to an early phase of sampling, whereas Kallmann may have included all twins as index cases who had been or were currently hospitalized. At any rate, in future studies these criteria should be specified in detail so that the rationale underlying them can be properly evaluated. The higher concordance rate for MZ twins reported by Kallmann (about 86 per cent) as compared to that reported by the other investigators (about 67 per cent) is due in most part to the difference between them just cited.

OL.
1
62/63

To this stage of the study, the investigator's life has been relatively easy. He must now locate the cotwins of the index cases and determine if the pairs are MZ or DZ (dizygotic), concordant or discordant. His search is likely to be long and arduous, and he invariably finds that a number of the cotwins have died, that others have emigrated from the area or cannot be contacted, and that a few may refuse for one reason or another to cooperate in the study. The investigator has the option of excluding these twin pairs from his study, but this may introduce some systematic bias of which he cannot be aware at this point, and may reduce the number of cases which (except possibly for Kallmann's sample) is already smaller than he would like. The tendency then is to retain as many pairs as possible by getting as much information as one can about all pairs of twins and making one's best judgment about zygosity and concordance for each pair.

If the cotwin has died, it is important to find out when he died. If death occurred before a stipulated minimum age of risk with respect to contracting schizophrenia, the pair must be excluded from the study since it cannot be known if the cotwin would have developed the illness or not. If death occurred at some time after the minimum age of risk, then the investigator must try to find out if the cotwin had been schizophrenic. If the cotwin had been seen at a clinic or admitted to a hospital, the records could be helpful in deciding if the pair was concordant. If not, the investigator must rely solely on the testimony and report of relatives and friends, who of course may be not adequately qualified observers. Such persons may overlook odd or bizarre behaviour as mere quirks of personality. On the other hand, they may see strangeness and disorder in behaviour which might not have been deemed inappropriate if the circumstances surrounding it had been known, or may make interpretations of that behaviour which may merely be reflections of their own personality disturbances or of their conviction that MZ pairs must be alike in disturbance as well as appearance.

The cotwin, living or dead, may not have given any indication of ever having had a schizophrenic illness, but at the time of the study he may not yet have lived through the period of risk. If, for example, such a cotwin were only 25 years old, should he be counted as discordant? He might well become a schizophrenic before very long, as far as one can know.

Kallmann used the abridged Weinberg method to deal with this problem. The age of risk was assumed to be from 15 to 44 years. If a twin pair was within this age range, it was counted as half a pair, so that two such pairs were counted as equivalent to one pair. This is a reasonable enough solution on the face of it, but it is unsatisfyingly crude and probably is not appropriate for twins. Moreover, it probably leads to an underestimate of the *dis*cordance rate in Kallmann's sample since he started initially with a resident hospital population which probably included a large number of chronically ill patients and waited nine years before accumulating the material in his 1946 article. According to MALZBERG[19], half of all new cases in New York State are on the average admitted by the age of 31·8 years, an age which most of the cotwins in Kallmann's study probably exceeded by the time he compiled his data, so that they would have passed through more than one-half the risk period.

Slater also applied the Weinberg abridged method to his sample. He used a *shorter* risk period than Kallmann's (age 14 to 40) which would thereby result in *less* of a correction than with the longer risk period. He had forty-one index MZ twin pairs in his sample among whom twenty-eight pairs or 68·3 per cent were considered to be concordant. Since twenty-three cotwins still had not reached age 41, each of these was counted as half a case, or 11·5 pairs altogether. To calculate the age-corrected concordance rate, the 11·5 " pairs " were added to the eighteen pairs who had reached age 41, making 29·5 pairs in all. Among these, then, were found twenty-eight concordant pairs, or 28/29·5, or 94·9 per cent. The latter represents the "corrected" concordance rate by this method, a figure which Slater discarded as having little meaning.

Slater believed that the Weinberg shorter method could not be applied to twins since they did not constitute an ordinary sample of the population. He also agreed with Schulz that it was logically incorrect to apply the correction only to discordant pairs (which would have yielded a corrected concordance rate of 74·7 per cent). Instead, he devised another method which took into account the correlation among his concordant twin pairs with respect to age of onset. This method seems to have a firmer empirical basis and it yielded a more acceptable estimate of concordance in Slater's sample (76·3 per cent), yet one which was actually very close to the rejected estimate which corrected for discordant pairs only.* The problem nevertheless remains theoretically unsolved, but it is not serious enough to challenge the validity of the twin method.

Although the age of the twins in his sample will pose problems for him, the investigator first must face the more important task of determining the zygosity of each pair of same-sexed twins in his sample. In all five studies, such determinations have been made by the "similarity method." In this method, both twins are compared with respect to a number of physical characteristics such as color of eyes, hair, skin, facial resemblance, finger-prints etc. The greater the number of traits on which both twins are similar, the more likely is the determination to be MZ. The task is easier if both twins can be seen together, but such simultaneous comparisons are not nearly as common as one would like, for various reasons. Even if both members of a pair can be seen separately, the investigator usually has a sense

* Kallmann must have applied the correction to discordant pairs only, or his estimated morbidity risk would have been considerably higher than his cited figure of about 86 per cent.

VOL.
1
1962/

of confidence in his ability to make the determination. When the cotwin is not available for personal evaluation, the investigator must rely on the testimony of relatives and friends or on photographs of the twin pair if these are available.

It is reasonable that under such conditions, investigators will have varying degrees of uncertainty about a number of pairs in their sample. The number will probably depend on the stringency and level of criteria which each investigator holds for himself, on the number of complete pairs which he is able to examine personally, and his confidence in the perceptiveness of those persons providing testimony. Essen-Möller's total series of twins consisted of sixty-nine pairs; among these he was able to examine personally both members of forty-one pairs, but only fifteen of these simultaneously, one member among nineteen pairs, and neither member among nine pairs. This appears to be the most complete series of personal examinations by an investigator among the five studies. Essen-Möller felt that he could make zygosity determinations "with more or less certainty" among all but two pairs of whose zygosity he was "especially uncertain". Rosanoff *et al.* stated that although "all error concerning this point could hardly be avoided, we believe any error thus incurred . . . to be on the whole so slight as to be negligible". Luxenberger appears to have been more cautious in this respect. Among forty-five same-sexed twin pairs with the index case diagnosed schizophrenic, he excluded fifteen pairs or one-third from consideration because he was doubtful of their zygosity. Slater had some question about the zygosity of sixteen among the thirty-seven pairs he called MZ with the index case diagnosed schizophrenic. In an additional two pairs, his uncertainty was greater and these were excluded from his series. Kallmann does not seem to have discussed these matters with respect to his sample, and has not indicated the number of pairs which had to be discarded on this account, if any.

In one of the most thorough applications of the similarity method in a twin study of psychopathology, EYSENCK and PRELL[20] compared *all* twins among fifty same-sexed pairs on fourteen criteria, among which were the blood groups A_1A_2BO, Rh, MNS, P, Lewis, Kell and Lutheran. Of the fifty pairs so evaluated, the authors still had some doubt about the zygosity of six pairs, or 12 per cent, a finding which suggests that a prudent course in such matters lies in the direction of conservatism.

Fortunately, it is possible for the investigator to check the representativeness of his sample with respect to the distribution of zygosity, as he has determined it. One well-established criterion of representativeness derives from the Weinberg Differential Method. This method assumes that the total number of DZ pairs in a population of twins will include an equal number of same-sexed and opposite-sexed pairs, since zygosity and sex are independent factors, and since the sex of any individual in a DZ birth will be proportional to the sex distribution among single births, or about 1:1. In actual practice, the assumption has repeatedly had empirical verification. Therefore, if one knows nothing more about the zygosity of same-sexed twins in a sample, one can estimate that the number of DZ pairs among these will be equal to the number of opposite sex pairs. The remainder should be an approximately correct estimate of the number of actual MZ pairs in the sample.

It is of interest to see how the five major studies compare in this respect. Table 2 shows the number of opposite-sexed pairs and same-sexed pairs said to be DZ in each sample. A chi-square test indicates that the studies differ significantly with respect to the proportion of opposite to same-sexed pairs. The samples of Rosanoff *et al.* and Slater are very close to

TABLE 2. FREQUENCY OF "DZ" TWIN PAIRS WITH A SCHIZOPHRENIC INDEX CASE, ACCORDING TO SAME OR OPPOSITE SEX

Study	Opposite Sex	%	Same Sex DZ	Total	Opposite Sex: Same Sex
Luxenburger (1928)*	20	60·6	13	33*	1·54: 1
Essen-Möller†	37	59·7	25	62	1·48: 1
Rosanoff *et al.*	48	47·5	53	101	0·91: 1
Slater	54	49·1	56	110†	0·96: 1
Kallmann (1946)	221	42·7	296	517	0·75: 1
Total	380	46·2	443	823	0·86: 1

Chi-square = 10·75, $p < 0·05$.
* 15 pairs of doubtful zygosity omitted.
† 2 pairs of doubtful zygosity omitted.

theoretical expectancy. Luxenburger's sample seems to deviate too much, but probably this merely reflects the fact that fifteen same-sexed pairs of doubtful zygosity are excluded, and that at least some of these are really DZ. Essen-Möller's sample has a slight excess of opposite-sexed pairs, but the difference is within the limits of expected sampling variation for a sample of this size. The sample which contributes most to the large chi-square is Kallmann's; the deviation from expected equality in this sample is significant at well beyond the 0·01 level, suggesting that either sampling errors or errors of zygosity determination have occurred.

According to Kallmann's evaluation, there were 174 MZ pairs in his sample. But since he had 470 same-sexed pairs altogether, the estimate of the number of MZ pairs in his sample by the Weinberg Differential Method would have been 249, a considerable difference.

The discrepancy may be explained in either of two ways, and in fact both may be contributory.

(1) There may actually be too few opposite-sexed pairs in the sample, as Kallmann believes. This could be due to cooperating hospital personnel singling out same-sexed pairs to be reported, or perhaps by failing to understand that opposite-sexed pairs are also twins. As indicated above, when sampling errors of this nature occur, they tend to involve over-reporting of concordant pairs (opposite-sexed pairs have the lowest concordance rate among twins[1]) and of MZ pairs. The finding, however, of *fewer* MZ pairs than the number to be expected by the differential method suggests that reporting errors do not account wholly for the difference. Moreover, the number of opposite-sexed pairs in the sample is 32 per cent of all pairs, which is very close to the "one-third" usually to be expected in this country.[18]

(2) Error may have been made in the direction of calling many pairs DZ when in fact they were really MZ. Error in this direction would not be surprising, since in many cases Kallmann probably had to rely on lay testimony to evaluate zygosity. With such a large

VOL. 1 1962/

sample it is difficult to see how he could personally evaluate as large a proportion of complete pairs as did the other investigators. Essen-Möller cites a study of non-psychiatric, same-sexed twins in which he evaluated direction of error when lay testimony was used as an aid in zygosity evaluation. When discordance of blood groups was used as the criterion of dizygosity, and the presence at birth of a single chorion was used as the criterion of monozygosity, it was possible on the basis of lay testimony to classify sixty-four of sixty-five DZ pairs correctly, but only thirty-one of forty MZ pairs correctly. Thus, errors consisted mainly in classifying MZ twins as DZ. If in fact this kind of error did occur in his sample, then a sizeable number of pairs called DZ by Kallmann may in fact have been MZ, and since most by far of these pairs were discordant, if they had been included with the MZ group the concordance rate for MZ twins would have been reduced appreciably in his sample.

OL.
1
62/63

Sampling errors may lead us not only to overestimate the proportion of variance in the etiology of schizophrenia which is contributed by heredity, but to overestimate the variance due to environmental factors as well. For example, Kallmann divided his MZ twins into pairs which had been separated for five or more years prior to the onset of schizophrenia in the index twin and pairs which had not been so separated. The corrected concordance rate for the separated pairs was about 14 per cent less than that for the non-separated pairs. Some psychodynamically minded persons have cited this finding as an indication of how important environment is in the etiology of schizophrenia, and JACKSON[2] has suggested that if the separation had occurred during the twins' formative years, the reduction in the concordance rate would probably have been much greater.

This may be so, but it is easy to visualize how such a finding could have been produced merely by not having strict control over all aspects of sampling. We have only to make the credible assumption that when both members of a twin pair (especially MZ twins) are patients in the same hospital, the probability of the pair being detected and reported by hospital personnel is disproportionately greater than when only one twin is a hospital patient. With respect to discordant pairs, the rate of reporting twins would be the same for both separated and non-separated pairs since in either case only one of a pair would be a resident patient. With respect to concordant pairs who are separated, the chance of a twin being reported would be no better since the twins would reside in different hospitals, whereas concordant pairs who are not separated would likely be admitted to the same hospital and would therefore be that much more likely to be reported. Thus, the number of discordant pairs would probably be about the same for both the separated and non-separated groups, but the increased number of concordant pairs reported among the non-separated pairs as compared to the separated pairs would make for a misleadingly higher concordance rate in the non-separated group.

Until it can be shown that the difference in concordance rates for the two groups found by Kallmann was not due to such sampling errors, it is prudent to have reservations about any theoretical implications of this finding.

PROBLEMS OF DIAGNOSIS

The logic of the twin studies involves two dichotomous variables. (1) Zygosity (MZ or DZ); (2) Diagnosis (schizophrenia or not schizophrenia). The relationship between them

is that of dependent variable (diagnosis) to independent variable (zygosity). For the present we need not consider whether the hereditary factors which may be implicated in schizophrenia or the behavioral characteristics on which the diagnosis is based are in fact continuously distributed, since our focus in this paper is methodological.

In any study which involves the relationship between two variables, it is axiomatic that the measurements of each should be made independently. Unfortunately, in the major twin studies of schizophrenia such separation of measurement has not occurred, mainly because three of the five studies were carried out by a single investigator who for the most part had to make the decisions about both zygosity and diagnosis personally. Despite one's best intentions, in cases of doubt with respect to the dependent variable, prior knowledge of determinations regarding the independent variable is likely in any instance to influence one's judgment regarding the dependent variable. That is why such great pains are taken in all experimental studies involving judgments about behaviour to maintain strict separation of measurement. In the twin studies, investigators conceivably could have called some doubtful pairs concordant because they knew the pairs were MZ or they could have "leaned over backwards" and called some such pairs discordant for the very same reason.

VOL.
1
1962/

In future investigations, it would be desirable to have one person or group of persons responsible for the determinations of zygosity, and at least two persons responsible for making diagnoses, no person making the psychiatric diagnosis of both members in any given pair. There should be no communication about cases among investigators, and procedures should allow for the possibility of estimating the reliability of both zygosity determination and diagnosis for the particular sample. These are simple precautionary measures to reduce and to control error in these respects. Once zygosity and diagnosis have been decided, investigators may perform other studies which permit both patients to be examined together psychiatrically or psychologically.

Since all index cases in the five major studies were obtained from hospitals, they were already carrying a diagnosis at the time they came under the scrutiny of the investigator. Often the investigators found it necessary to change these diagnoses, but we do not know how often. In the end, each investigator reevaluated his index cases according to his own diagnostic criteria. Since the initial selection of index cases was without regard to diagnosis, the entire pool of index twins was so reevaluated; a breakdown of the sample according to the investigator's own diagnosis is therefore possible, and the samples can be compared in this respect. It is of greatest interest to compare them with respect to the two disorders which often pose difficult problems of differential diagnosis, viz., schizophrenia and manic-depressive psychosis. The relevant data have been compiled and arranged as in Table 3.

It can be seen in Table 3 that the five studies are in sharp disagreement with respect to what is being called schizophrenia and to what is being called manic-depressive psychosis. The chi-square test of the differences among them reaches an extremely high value of 174·9 (at $p = 0{\cdot}001$, chi-square equals 18·46). The only two investigators who seem to be in agreement are Luxenberger and Essen-Möller, but even in these studies, when we compare the proportion of cases called schizophrenic to *all* other index cases in the sample (105 for Luxenburger and 110 for Essen-Möller) we find that these two investigators may also be disagreeing significantly on what they call schizophrenia (chi-square $= 4{\cdot}89, p < 0{\cdot}05$) unless there have been some peculiarities of sampling in their studies of which I am not aware.

Table 3. Number of all "twin index" cases in the samples diagnosed schizophrenia and manic-depressive psychosis

Study	Schizophrenia (SZ)	Manic-depressive (M-D)	Ratio (SZ: M-D)
Luxenburger (1928)	106	38	2·8: 1
Essen-Möller	69	23	3·0: 1
Rosanoff *et al.*	142	90	1·6: 1
Slater	158	23	6·9: 1
Kallmann (1950)	953	75	12·7: 1

Chi-square = 174·9, $p<0·001$.

OL.
1
62/63

Studies of the relative unreliability of psychiatric diagnoses have been reported several times before, and I do not wish to review this literature here or to labor this point. However, a solution to the problem is not furthered by ignoring it or by trying to convince ourselves that it is really not important. When we are trying to understand the role of heredity in mental illness, we must inevitably face the question of " heredity with respect to what? "—a question which is necessarily intertwined with the question of diagnosis.

One point suggested by Table 3 is that since the ratio of cases called schizophrenic to those called manic-depressive psychosis is highest in the two most recent studies (Kallmann and Slater), this may indicate a current trend toward calling more forms of psychiatric disorder "schizophrenia" and restricting the definition of "manic-depressive psychosis" more sharply.

Another factor influencing the ratios could be the kind of sampling procedure used. If one samples from resident hospital populations, the ratio should be relatively high since schizophrenic patients are more likely to become long-term hospital residents, whereas in the affective disorders, the prognosis is generally better and relatively more of such cases will be missed. If one samples from consecutive admissions as in the case of Essen-Möller and Luxenburger, the ratios should more closely approximate the actual frequency of hospitalization for these kinds of disorder. However, even when we separate the studies into the two groups which used different sampling procedures, we still find differences in ratios within the groups. The difference previously cited between Essen-Möller and Luxenburger however is relatively slight as compared to the extreme differences in the ratios of the three studies sampling primarily from resident populations.

Kallmann[21] was the only one of the five investigators who specified his diagnostic criteria of schizophrenia. They are of sufficient interest to warrant quoting:

". . . our diagnosis of schizophrenia rested on the constellative evaluation of basic personality changes observed in association with a whole group of possible psychopathological mechanisms, rather than on the presence of any particular type of symptomatology. As a general principle, greater diagnostic importance was attached to the demonstrable effect of a 'bending' curve of personality development than to any surface similarities to

pathognomonic textbook descriptions, especially when this bend was found in conjunction with such malignant features as xenophobic pananxiety, loss of the capacity for free associations, inability to maintain contact with reality (autistic and dereistic attitudes toward life), or a compulsive tendency to omnipotential thought generalizations".

This definition raises at least three points which deserve comment:

(1) The definition is very broad and gives the investigator wide latitude regarding the kinds of cases which he will call schizophrenic. It is this fact, as well as his restricted definition of manic-depressive psychosis, which reflects in good part the high ratio found in Table 3 for Kallmann as compared to the other investigators.

(2) The language specifying the criteria is, unfortunately, highly abstract and unusual.* Anyone who has engaged in studies of reliability would expect diagnostic reliability with such criteria to be of a low order. Concepts such as "constellative evaluation of basic personality changes, . . . bending curve of personality development, . . . xenophobic pananxiety, . . . loss of capacity for free associations, . . . compulsive tendency to omnipotential thought generalizations" . . . must indeed be hard to define and exemplify in any concrete way. On his behalf, it should be noted that Kallmann did have samples of twins reviewed by independent judges who were instructed regarding his criteria, but he did not make a systematic, statistical analysis of the reliability found. Moreover, Kallmann, in a personal communication, stated that he never made a psychiatric diagnosis alone. However, as might be expected, most of the diagnostic changes made were from manic-depressive and psychoneurotic categories to schizophrenia, but the relative number of such changes does not seem to have been large.

(3) One can point to two opposing current trends with respect to the diagnosis of schizophrenia. The first is represented by Kallmann and those whom he has followed. This trend is to loosen the boundaries surrounding the class of disorders called schizophrenic to include a wide variety of behavioral disturbances. The emphasis is on "personality change", whereas symptoms are thought to be superficial aspects of the disorder which do not, *per se*, have any special diagnostic significance. As Kallmann says, he was not concerned about "any surface similarities to pathognomonic textbook descriptions". Consequently, there is also less interest in subtypes with this orientation.

By contrast, another trend is to pay ever more careful attention to symptoms and to group them in clusters which define biologically distinct types. LEONHARD[22] is one of the best known exemplars of this orientation. By carefully observing and classifying patients over a period of many years, he concluded that there were three major types of schizophrenias called non-systematic, simple systematic and combined systematic. Each of the systematic groups had three major forms, and each form had several subtypes, all together making for twenty-seven subtypes with their own patterns of familial distribution. There are no formal reliability studies of this diagnostic system but FISH and ASTRUP[23] claim to have been successful in classifying patients in accord with it.

The contrast between the two opposing trends is of interest because we must be concerned with the question of what aspects of behavioral disorder are inherited. If Kallmann's

* In contrast, Kallmann's criteria for diagnosing manic-depressive psychosis are quite specific and clear, including only "cyclic cases which showed periodicity of acute, self-limited mood swings before the fifth decade of life and no progressive or residual personality disintegration before or after such episodes."

VOL.
1
1962/

scheme is used, the whole pattern of inquiry and inference will be different from that which occurs when a Leonhardian system is used. Questions with respect to pattern of genetic transmission and biological unity are fundamentally involved. Each system also has different heuristic implications with respect to manifestations of the disorder, but we cannot examine these in detail at this time.

Although the problems of diagnosis discussed to this point are clearly weighty ones, we have been talking mainly about diagnosis of the *index cases* in the five samples. However, the greatest difficulties around diagnosis arise with respect to the cotwins, especially those who have never been hospitalized or those who have been hospitalized but who cannot be evaluated personally by the investigator. It is especially in such cases that the individual making the diagnosis should have no knowledge of either the zygosity or diagnosis of the index twin. Although we have no information on this point, it seems likely that disagreements about the diagnosis of cotwins would be even more frequent than disagreements found in diagnosing index cases.

OL.
1
62/63

Although the index cases in all five studies have been hospitalized patients, no such restriction has been imposed on the cotwins called concordant. This procedure promotes a "double standard" which has the effect of increasing concordance rates unduly. The point may be difficult to grasp. Consider the sample of index cases and the sample of their cotwins as two separate distributions of disorders, the first having a relatively narrow range because of the restriction imposed by hospitalization, the second having a larger range which includes a wider variety of behavioral disorders. For the moment let us ignore the label "schizophrenia". If we select all possible alternatives from the second range as acceptable matches for the first (concordant), we increase the probability of calling any single pair concordant, the increase being proportional to the ratio between the sizes of the two ranges. The point becomes clearer if we reverse the order of imposed restrictions. Let us now assume that the index cases have been sampled to include all the classes of disorder which may be called schizophrenic, the sample obtained from outpatient clinics and the population at large as well as from hospitals. However, let us now decide that for a cotwin to be concordant, he must be hospitalized. This procedure obviously would decrease the obtained concordance rate in a completely unacceptable way, a way which merely reverses the order of the usual sampling procedure. In principle, the same standards or criteria of inclusion should be applied to both the index cases and the cotwins to avoid biasing the results in either direction.

The sampling procedure is itself an important factor with respect to the problem of diagnosis. When sampling is from a resident population with a large proportion of chronically ill patients, the diagnoses will probably be easier to make since the clinical conditions will have become relatively stabilized. When sampling occurs among more recent admissions, diagnostic problems are likely to be greater. Thus, FOULDS[24] and SCHMIDT and FONDA[25] reported good diagnostic reliability in studies done in public hospitals, whereas in a study done at a clinic, ASH[26] reported considerably poorer reliability. The importance of this factor can be seen in a comparison of three reports by Luxenburger who sampled from consecutive admissions in good part. Table 4 shows the number of MZ pairs said to be concordant and discordant in each report[8, 27, 28].

It can be seen in Table 4 that as the total number of MZ pairs reported increased during

TABLE 4. NUMBER OF CONCORDANT AND DISCORDANT MZ PAIRS AS EVALUATED BY LUXENBURGER IN THREE SUCCESSIVE REPORTS

Year	Concordant pairs	Discordant pairs	Uncorrected concordance rate
1928	13	4	76·5
1930*	14	7	66·7
1934†	9	18	33·3

Chi-square = 9·44, $p<0.02$

* This is the concordance rate which has been cited most frequently and is therefore best known.

† This report seems to have been overlooked. The only one I know who has called attention to it is ESSEN-MÖLLER[7] who seemed surprised and puzzled about it.

VOL. 1 1962/

the six-year interim, the number of pairs said to be concordant actually decreased while the number said to be discordant increased disproportionately. A chi-square test of the relative frequencies indicates that the proportions differ significantly. This point is of unusual interest since it is generally assumed that the opposite must be true, viz., that the concordance rate for a given sample must *increase* with time, if it changes at all. I do not know how to account for these data except to infer that Luxenburger changed his mind about the diagnosis of a sizeable proportion of his cases, especially those whom he had earlier called "probably schizophrenic".

The precariousness of diagnosis with such a sample can also be seen in Essen-Möller's series of consecutive admissions. In seven MZ index cases there seems to be little question that the diagnosis of schizophrenia applies. These are the ones reported by the author. However, four additional MZ index twins were said to be "not classical schizophrenics" but probably "in the sphere of psychoses hereditarily related to schizophrenia". In this country, these cases would likely be called schizophrenic by most diagnosticians. Two of the four twin pairs were clearly discordant, a third questionably discordant, the fourth probably concordant. In the two latter cases one would surely get diversity of opinion. When one reads the case histories of the cotwins, one gets a vivid picture of the contingencies which could make for some diagnosticians calling the concordance rate in this series as low as zero while others might determine the rate to be 75 per cent or higher, depending on the criteria used. Clearly, however, with respect to severity of the illness and symptomatology, concordance in this series is virtually zero. It is not surprising then that Luxenburger wavered so in diagnosing his own series of consecutive admissions.

DISCUSSION

The reader by now has some appreciation of the potential influence of sampling and diagnostic procedures on the results that can be obtained in twin studies, and the complexities

of the problems posed by each procedure. For example, it would be wrong to infer from this brief summary that in future studies one should not sample from consecutive admissions but from resident populations. I have discussed some of these issues more fully in a previous paper[17]. The latter method of sampling yields a sample biased in the direction of higher concordance with respect to both schizophrenia and the severity of the illness or symptomatology. A preferable procedure would be to sample extensively from consecutive admissions to both outpatient and inpatient facilities and to follow all cases until they had lived through the age of risk.

The problem of diagnosis would however remain with us, regardless of the sampling method used. In all probability, studies in the future will do well to include various kinds of objective tests, both as diagnostic aids and, in their own right, as indicators of what indeed may be the inherited factors. Based on the marked discrepancies in symptomatology among his MZ pairs, Essen-Möller concluded that what was inherited was a "characterological defect". If he is right, then what could this defect be?

OL.
1
62/63

One possible answer has been suggested by McConaghy[29]. He administered an object-sorting test to ten pairs of parents of schizophrenic patients with a thinking disorder. Although none of these parents had ever been hospitalized or diagnosed schizophrenic, in each of the ten pairs at least one parent showed peculiarities of thinking on this test which occur predominantly among schizophrenic subjects. This contrasted with a control group in which only about nine per cent scored at the "schizophrenic" level. I have thus far repeated this procedure with five pairs of parents who fitted McConaghy's criteria, and again in each pair at least one parent has scored in the schizophrenic range. Lidz and his colleagues, based on intensive interviewing of nonhospitalized parents of schizophrenic patients, had earlier reached the same conclusion: that a high rate of thought disturbance existed among such parents[30].

The implications of these findings may be of the utmost consequence for understanding the etiology of schizophrenia. On the one hand, it may be that schizophrenia occurs as a learning process, the future patient being receptive to and amplifying the peculiar thought patterns of a given parent. Lidz's concept of the "transmission of irrationality" points to the possibility that some such process occurs. On the other hand, it may be that a characteristic pattern of disturbed thinking is being mediated through a genetically determined mechanism which is passed on directly from parent to child. In either case, we are confronted with the problem of why the child is overtly schizophrenic and the parent is not, or why one MZ twin shows marked thought deterioration and the other does not. This is clearly a challenging problem for further study.

If what is inherited "characterologically" is such a thinking disturbance, then from a genetic point of view the pattern of transmission would appear to be a dominant rather than a recessive one. These matters of course require further investigation and I am currently engaged in a study of them.

In the context of such thinking, the important question must be raised about the value of figures cited in the past to indicate the incidence of schizophrenic disorder among relatives of schizophrenic patients. If one bases estimates of incidence among the parents of schizophrenics primarily on hospitalization figures, the rate will be relatively low: 9·2 per cent, Kallmann[10]. If estimates are based on intensive clinical examination of the parents, as in

the studies by LIDZ *et al.*[30] and SACKLER *et al.*[31], the rates increase ninefold to about 80 per cent. When one considers such differences, plus the marked influences of various sampling procedures and diagnostic leanings, it is not surprising that no consensus has been obtained regarding the pattern of genetic transmission in schizophrenia. Whereas the problems of sampling and diagnosis are troublesome enough in twin studies of schizophrenia, they are compounded to an unknown degree in most other studies of familial incidence.* That is why I believe that the best information we now have, with respect to the whole broad question of heredity and environment in schizophrenia, is to be found mainly in the five major studies of twins.

It would be wrong to conclude from this critical evaluation of the twin studies that there is no worthwhile evidence for a genetic contribution to the etiology of schizophrenia. The total weight of the evidence from all studies still strongly favors such an hypothesis, despite their weaknesses. All data are fallible. Our task is to determine their source, extent and implications, not to dismiss them offhandedly because they contain errors. What does appear to be the case is that heredity does not account for as much of the variance with respect to what is called schizophrenia as some have alleged. In an earlier paper, I pointed out in an analysis of Slater's twin series that at least one group of schizophrenias could be shown to have little or no genetic basis at all, although in a second group there seemed to be a high genetic loading[32].

It is to such problems that we must address ourselves. If we keep in mind that what is called schizophrenia is probably not a unitary disease, biologically speaking, that sampling procedures must be exceptionally rigorous, that criteria of diagnosis must be specified in reliable detail, that rating and testing procedures should be liberally employed, that future research should be hypothesis-oriented and that both hereditary and environmental factors are probably contributing in varying degree to different types of the disorder, we may only now be on the threshold of discovery with respect to the basic issues surrounding the origin and transmission of schizophrenic behavior.

SUMMARY

Problems of sampling and diagnosis in the five major twin studies of schizophrenia are critically reviewed. The main pitfalls and inconsistencies between the studies are indicated, and recommendations are made regarding methods of handling these problems. It is pointed out that despite their difficulties and errors, the twin studies probably have contributed our most reliable data regarding the inheritance of schizophrenia. On the basis of this review, one could conclude that the proportion of the variance contributed by heredity with respect to those disorders called schizophrenic is probably less than some have alleged, and that we may only now be at the point of being able to expand our knowledge of these matters in a heuristically important way.

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* Although in other family studies, the problem of zygosity determination does not occur, the investigator has to examine an extremely large number of relatives if he is not to rely on gross criteria; a disproportionate number of relatives emigrate or cannot, or will not, participate in the study for all kinds of reasons, especially collateral relatives; the lines of descent are not always certain because the paternity in a number of instances cannot be guaranteed; and the investigator has no way of knowing if his sample is representative.

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VOL.
1
1962/

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THE ASSOCIATION BETWEEN SELF-ESTEEM AND ANXIETY

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OL.
1
62/63

1. INTRODUCTION

IN RECENT years, the fields of psychiatry, psychology, and sociology have all experienced an upsurge of interest in the nature of the self-image. The fact that these three fields, differing as they do in their subject matter, research methods, perspectives, and foci of interest, should come to share an interest in this aspect of personality bespeaks, perhaps, the power of this concept to intrude itself upon established ways of thought and procedure. Though each field bears with it the inertia of its distinctive tradition, all have found that the idea of the self-image is, if not central to their concerns, at least relevant to them.

The self-image is, of course, a complex concept. In this paper, we will consider one aspect of this concept, *viz.*, the individual's self-esteem, the degree to which he holds attitudes of acceptance or rejection toward himself. It is one of the peculiarities of the self, as MEAD[1] has noted, that the self is reflexive, that the self is both subject and object, that the judge and the object to be judged are encased within the same skin. Every individual has attitudes towards a multitude of objects in the world, and one of these objects — probably the most important — is himself. It is this favorable or unfavorable attitude toward oneself that we designate by the term self-esteem.

There is ample clinical and theoretical warrant for expecting the individual's level of self-acceptance to have certain emotional consequences. Some clinicians go so far as to characterize low self-esteem as one of the basic elements of neurosis. HORNEY[2] and FROMM[3] stress that an underlying feeling of worthlessness is characteristic of the sick personality. A psychotherapist, ANGYAL[4] states: "In the neurotic development there are always a number of unfortunate circumstances which instill in the child a self-derogatory feeling. This involves on the one hand a feeling of weakness which discourages him from the free expression of his wish for mastery, and on the other a feeling that there is something fundamentally wrong with him and that, therefore, he cannot be loved. The whole complicated structure of neurosis appears to be founded on this secret feeling of worthlessness, that is, on the belief that one is inadequate to master the situations that confront him and that he is undeserving of love . . .".

One reason that low self-esteem may be related to certain symptoms of emotional disturbance is that, in MURPHY'S[5] view, the self-image is central to the individual's value system. "Whatever the self is," he says, "it becomes a center, an anchorage point, a standard of comparison, an ultimate real. Inevitably, it takes its place as a supreme value . . . . To most

men in most societies, the self may be full of blemishes, of sin, of incompetence, but it is the one beloved self, the lawgiver. In a fundamental sense, the self is right."

A "good self," then, irrespective of its basis, is postulated as a universal value. If the self is a value, an irreducible good, then we would expect a negative self-opinion to be associated with certain signs of emotional disturbance.

The present paper focuses on one major expression of emotional disturbance, *viz. anxiety*. Recent psychiatric theory has manifested a growing tendency to assign to anxiety an important, if not central, position in psychopathological development. Indeed, it may not be extravagant to contend that no theory of neurosis can be considered adequate or complete which fails in some way to take account of this emotional state.

2. THE ASSOCIATION BETWEEN SELF-ESTEEM AND ANXIETY

The association between self-esteem and anxiety was investigated by means of questionnaires administered to 5,077 high school juniors and seniors in a stratified random sample of ten high schools in New York State. Three separate but overlapping questionnaire forms were used; much of the material on each of these forms was similar, but some of it was different. Some of the data, then, will be based on two-thirds of the sample and some will be based on one-third. Wherever possible the largest number of cases available is reported.

The measure of "self-esteem" employed in this study is a ten-item Guttman scale; the reproducibility of this scale is 93 per cent and its scalability is 72 per cent.*

"Anxiety" was indexed by reports of secondary physiological symptoms. It is well known that the impingement of a fear-arousing stimulus produces an elevated level of adrenalin which is functional for coping with emergency conditions.[9] Anxiety may be considered a more or less chronic and unfocused state of fear, less intense perhaps than acute fear but more sustained in its action and less appropriate to the objective stimulus. Hence, anxiety has typically been found to produce a variety of secondary physiological reactions — heart pounding, trembling, palmar perspiration, shortness of breath, a general feeling of nervousness, etc. If people with low self-esteem do indeed feel a higher level of anxiety, then we would expect them to be more likely to experience these secondary physiological symptoms.

The respondents were asked to report the frequency with which they experienced the following symptoms: trouble in getting to sleep and staying asleep; hand trembling, nervousness, heart beating hard, pressures or pains in the head, fingernail biting, shortness

*The items used in this scale, with which the respondents were asked to strongly agree, agree, disagree, or strongly disagree, were the following: (1) On the whole, I am satisfied with myself; (2) At times I think I am no good at all; (3) I feel that I have a number of good qualities; (4) I am able to do things as well as most other people; (5) I feel I do not have much to be proud of; (6) I certainly feel useless at times; (7) I feel that I'm a person of worth, at least on an equal plane with others; (8) I wish I could have more respect for myself; (9) All in all, I am inclined to feel that I am a failure; (10) I take a positive attitude toward myself.

Since a number of "contrived items" were utilized in the development of the scale, the eleven-point scale has been condensed into a seven-point scale. The logic of the Guttman scale appears in STOUFFER[6]; the scalability measure is discussed in MENZEL[7]; the method of "contrived items" is presented in STOUFFER *et al.*[8]

There are some data to suggest that this scale is moderately reliable. Among fifty students who filled out these scales 9 months apart, 80 per cent either had identical scores or were within one step of their original scores on this seven-point scale.

VOL. 1 1962/

of breath when not exercising or working hard, hands sweating, sick headaches, nightmares, "cold sweats", fainting spells, dizziness, and upset stomach.

The results indicate that in every case there is a tendency for those with lower self-esteem to be more likely than others to experience these symptoms. In some cases the relationship is extremely strong and regular, in other cases it is weaker and somewhat irregular. But in all cases the general pattern prevails. Certain of these symptoms appear so infrequently in the entire sample that there is little opportunity for discrimination between the high and the low self-esteem respondents. The strongest relationships appear between self-esteem and symptoms of insomnia, hand trembling, nervousness, heart pounding, head pressures or pains, and palmar perspiration; somewhat weaker relationships with fingernail biting, shortness of breath, sick headaches, nightmares and "cold sweats"; and the weakest (but still positive) relationships with fainting, dizziness, and upset stomach (partly because so few report these symptoms with great frequency).

OL.
1
62/63

But how useful are these self-reported physiological symptoms as indicators of anxiety? First, it is interesting to note that the symptoms most strongly related to self-esteem are those which are most commonly associated with free anxiety clinically. Secondly, it has been found that the self-reports of these physiological symptoms are valid and powerful discriminators of neurosis within a large but special group of subjects. During World War II, social scientists working in the Research Branch of the Information and Education Division, U.S. Army, attempted to develop a paper-and-pencil screening instrument which would differentiate certified neurotics from effectively functioning soldiers.[10] Specifically, the groups compared were the following: (1) a criterion group of soldiers diagnosed as psychoneurotic, whose psychological malfunctioning was so serious that they could no longer carry on their duties and were hospitalized as a consequence (the criterion group was defined as "those men who proved incapable of serving usefully in the Army because of psychoneurosis"), and (2) a cross-section of soldiers "selected in accordance with the sampling procedures usually employed by the Research Branch"[10]. There were 563 neurotic patients and 3,501 normal soldiers in the study. Fifteen areas, using over 100 personality, attitude, and background items, were used in the questionnaire. It was found that "psychosomatic complaining was the area which most sharply differentiated between the normals and neurotics"[10]. In fact, on the basis of a factor analysis, it was found "that the single area of psychosomatic complaints would discriminate about as well as the entire combination of fifteen areas". The results showed that a "simple dichotomous scale scoring of the psychosomatic complaints area alone resulted in 29 per cent of the nonpsychoneurotics and 93 per cent of the psychoneurotics in these subsamples receiving critical scores"[10]. Within the groups studied, then, these self-reported secondary physiological manifestations did differentiate between normals and neurotics with great power and effectiveness.

These psychosomatic items are the ones used in this study. Only one of the fifteen items has been omitted. In order to make our data as closely comparable to the Research Branch data as possible, we have dichotomized our items and scored them exactly as they did. Table 1 shows the relationship between self-esteem and these physiological indicators of neurosis. Without exception, each step down the self-esteem scale produces a larger proportion of respondents with many physiological symptoms. At the extremes the differences

are particularly great. Whereas 59 per cent of the highest self-esteem group had few symptoms, this was true of only 16 per cent of those with the least self-esteem.

TABLE 1. SELF-ESTEEM AND PHYSIOLOGICAL INDICATORS OF "NEUROSIS"*

Number of psychosomatic symptoms	Self-esteem						
	High 0	1	2	3	4	5	Low 6
1 or less (%)	59	50	41	37	28	19	16
2–4	35	40	44	46	44	50	42
5 or more	5	11	16	18	29	32	43
Total (%)	100	100	100	100	100	100	100
Number	(516)	(866)	(784)	(506)	(265)	(126)	(38)

*Employed by the Research Branch, Information and Education Division, U.S. Army[10]

This already strong relationship can be made even sharper if ten out of these fourteen symptoms are selected for consideration.* Table 2 shows that fully 71 per cent of those highest in self-esteem, but only 13 per cent of those lowest in self-esteem, experienced two or fewer symptoms. Conversely, 68 per cent of the latter, compared with 18 per cent of the former, reported four or more symptoms.

TABLE 2. SELF-ESTEEM AND FREQUENCY OF REPORT OF PSYCHOSOMATIC SYMPTOMS

Number of psychosomatic symptoms	Self-esteem						
	High 0	1	2	3	4	5	Low 6
2 or less (%)	71	58	46	41	31	22	13
3	12	15	16	17	14	18	18
4 or more	18	29	39	42	56	60	68
Total (%)	100	100	100	100	100	100	100
Number	(518)	(872)	(786)	(509)	(268)	(126)	(38)

*The four omitted are fainting, dizziness, "cold sweats," and upset stomach. Probably the reason fainting and dizziness discriminate less well in this sample than in the army study is that half of our sample are female, in contrast to the all-male army sample. Because of cultural factors, it may be a less serious sign of psychological malfunction for a female to report ever experiencing fainting and dizziness than a male; this might account for the weakening of the relationship. The other two items were reported so rarely in the total sample that they could not powerfully differentiate groups in terms of neurosis.

VOL 1 1962

In order to bring additional evidence to bear on this question, a list of "ailments" which are often thought to have psychogenic components was presented to the respondents, and they were asked to indicate how much they had been bothered by such ailments during the past five years. People with high and low self-esteem differed in reporting "nervousness", "loss of appetite", "insomnia", and "headache"— items which, it may be noted, were similar to some appearing in the psychosomatic symptom score. The results indicate that as self-esteem declined, the proportions reporting being bothered by three or more of these ailments were 15 per cent, 18 per cent, 24 per cent, 22 per cent, 33 per cent, 37 per cent, and 64 per cent.

The respondents were also asked which of the following ailments had required medical attention during the past five years — headache, nervousness, nausea, and loss of appetite. Whereas 17 per cent of those with the highest self-esteem said that any of these had required medical attention: this was true of 30 per cent of those with the lowest self-esteem*.

Since the psychosomatic score is a better validated measure than the list of ailments (in terms of its ability to discriminate between neurotics and normals), attention will be confined to this measure†. Properly speaking, the psychosomatic symptoms have been validated as an index of "neurosis" in a selected group, but we are rather inclined to treat them as indicative of anxiety. There is no inconsistency in this interpretation if it be assumed that virtually all neurosis is characterized by conscious or unconscious anxiety. Neurosis does generally include anxiety, but it probably includes other things as well: distortions of reality, inappropriate reactions or responses to situations, domination by unconscious needs, disturbances in interpersonal relations, inadequate functioning in other areas of life, etc. Anxiety is, then, probably a necessary but not a sufficient condition for neurosis.

In addition to these physiological indicators, FROMM-REICHMANN[11] has suggested that anxiety is manifested by (1) "interference with thinking processes and concentration," (2) "a frequently objectless feeling of uncertainty and helplessness," (3) "intellectual and emotional preoccupation," and (4) "blocking of communication." Some of our items appear to reflect these states in some measure. The statement "I find it hard to keep my mind on a single task or job" appears to indicate an interference with concentration. "I feel anxious about something or someone all the time" suggests a feeling of uncertainty. "At times I have been worried beyond reason about something that really did not matter" would appear to reflect intellectual and emotional preoccupation. And a negative response to the statement "I find it easy to make talk when I meet new people" would suggest a blockage of communication. All of these indicators are, to be sure, very crude measures

*There is also evidence to suggest that people with low self-esteem are more likely to be seen by others as depressed. In a special study involving a small sample of fifty-three subjects, observers who had no knowledge of the subjects' self-esteem scores filled out forms describing the subjects. People with low self-esteem, it turned out, were significantly more likely than those with high self-esteem to be described by others as "often gloomy" and "frequently disappointed."

†It is, of course, reasonable to contend that soldiers in wartime service are very different from students in high school. Hence, symptoms which are indicative of neurosis in the former group may not be symptomatic of neurosis in the latter. Nevertheless, the physiological theory which interprets these symptoms as indicative of anxiety would apply to both groups equally and is reasonably likely to reflect certain qualities typically associated with neurosis. Whether it does so perfectly for the group under consideration cannot be ascertained at this point, but it is almost inconceivable, in light of the Army Research Branch evidence, that it can be entirely irrelevant.

of the concepts advanced by FROMM-REICHMANN. Unlike the psychosomatic symptoms, furthermore, they have not been validated against an external criterion; hence, the findings must be thought of as suggestive at best. It is interesting to note, however, that with regard to *every one of the indicators of anxiety cited*, people who were low in self-esteem, according to our measure, were more likely than those with high self-esteem to report having such experiences. While each of these indicators is undoubtedly questionable in itself, the consistency of these results merits serious consideration.

3. CONTRIBUTORY FACTORS

Given the association between self-esteem and anxiety, the question arises: Does low self-esteem tend to generate anxiety or does anxiety tend to generate low self-esteem? Horney, on the basis of her clinical and theoretical work, has taken the position that anxiety is of central significance; her position is that anxiety sets in motion a complex chain of psychological events which produces, among other consequences, self-hatred and self-contempt. Briefly, Horney contends that the child, through a variety of adverse circumstances in the family, develops a fundamental fear, a basic anxiety. In order to cope with this anxiety, he retreats into the world of imagination where he creates an idealized image which gives him a sense of strength and confidence. This image is so admirable and flattering that when the individual compares it with his actual self, this latter self is so pale and inferior by comparison that he feels a hatred and contempt for it.

In this view, then, anxiety tends to generate low self-esteem. There is reason to believe, however, that the opposite sequence may also occur, *viz. that low self-esteem may generate anxiety*. This can occur for reasons quite different from those advanced by Horney. This point will thus constitute the central focus of the remainder of this discussion. In the analysis which follows, we will attempt to specify certain factors associated with self-esteem, disturbances in which may reasonably be expected to create anxiety. Four such factors will be considered: (1) instability of self-image, (2) the "presenting self", (3) threats to the self-image, and (4) feelings of isolation. We hypothesize that low self-esteem contributes to these four conditions, and that these conditions in turn tend to generate anxiety.

Instability of the self-image

One possible reason why people with low self-esteem experience an inordinate amount of anxiety is that they may tend to have shifting and unstable self-pictures. Table 3 shows the

TABLE 3. SELF-ESTEEM AND STABILITY OF SELF-PICTURE

"Stability of self-picture" score	Self-esteem: High 0	1	2	3	4	5	Low 6
Very stable (%) 0–1	71	46	35	20	15	19	21
Intermediate 2	20	28	33	31	29	27	37
Very unstable 3–5	10	26	33	49	56	54	42
Total (%)	100	100	100	100	100	100	100
Number	(484)	(811)	(740)	(460)	(249)	(121)	(38)

relationship between the individual's score on the self-esteem scale and his score on a "stability of self-picture" scale.* Two points should be made about this table. The first is that the least stability is found among those who have rather low self-esteem, but not the lowest. The relationship is somewhat curvilinear, with the trough appearing among those who have fairly low self-esteem (score 4 on the self-esteem scale). In other words, it is those who hold rather negative opinions of themselves, but who are not absolutely, unequivocally, consistently self-deprecatory who have the most changeable pictures of themselves.

The other point is this: people with low self-esteem are much more likely than those with high self-esteem to have unstable self-conceptions. At the extremes, the people with high self-esteem were three-and-one-half times as likely as the people with low self-esteem to have "very stable" self-pictures and the latter were four times as likely as the former to be "very unstable."

OL.
1
62/63

Why low self-esteem should be associated with an unstable self-picture will be discussed later. At this point we wish to discuss another question. It has been shown that people with low self-esteem are more likely to experience symptoms of anxiety, and that these people are also more likely to have unstable self-pictures. The question now becomes: Are people with unstable self-pictures more likely to experience anxiety?

Frame of reference theory leads us to expect this to be the case. SHERIF[12] has provided striking demonstrations of the fact that it is characteristic of the human mind to assimilate new experiences or stimuli into already existing frames of reference. It seems reasonable to assume that the individual's self-attitude is probably the major single anchorage point to which new stimuli are related. How can a man decide what to do without taking account of what he is like?

The point, then, is this: If an individual has unclear, unstable, uncertain opinions, attitudes, and perceptions of himself — if he simply is not sure of what he is like — then he is deprived of his most valuable frame of reference; this deprivation is almost certainly anxiety-provoking, and the data support this reasoning. Table 4 shows that the more uncertain the individual is about what he is like, the more does he tend to report experiencing many physiological symptoms of anxiety. For example, 66 per cent of those with stable self-pictures had few psychosomatic symptoms compared with 32 per cent of those whose pictures were unstable.

The results thus indicate that people with low self-esteem have less stable self-pictures, that people with unstable self-pictures have more psychosomatic symptoms, and that people with low self-esteem have more psychosomatic symptoms. But in order to be able to say that people with low self-esteem are more anxious because their self-pictures are more unstable, it is necessary to show that were they not more unstable — were the stability of all groups in fact equal — then they would not have more psychosomatic symptoms than others (or that the difference between the groups would decrease). In order to examine this

*The reproducibility of this scale was 94 per cent and its scalability was 77 per cent. The scale consisted of the following items: (1) Does your opinion of yourself tend to change a good deal or does it always continue to remain the same? (2) Do you find that on one day you have one opinion of yourself and on another day you have a different opinion? (3) I have noticed that my ideas about myself seem to change very quickly. (4) Some days I have a very good opinion of myself; other days I have a very poor opinion of myself. (5) I feel that nothing, or almost nothing, can change the opinion I currently hold of myself.

question, we have equated the stability of all self-esteem groups by "standardizing" on stability.*

TABLE 4. STABILITY OF SELF-IMAGE AND FREQUENCY OF REPORT OF PSYCHOSOMATIC SYMPTOMS

Number of psychosomatic symptoms	"Stability of self" scale					
	Stable 0	1	2	3	4	Unstable 5
2 or less (%)	66	58	50	39	32	32
3	13	15	14	19	15	14
4 or more	21	27	37	43	53	54
Total (%)	100	100	100	100	100	100
Number	(388)	(760)	(848)	(633)	(239)	(91)

Table 5A shows the original relationship between self-esteem and psychosomatic symptoms, and Table 5B shows the relationship which would appear if all groups were equal in stability. It will be seen that were all groups equal in stability, the relationship between self-esteem and psychosomatic symptoms would decrease, although it would still remain strong. Originally, for example, those with the highest self-esteem were 50·2 per cent more likely

TABLE 5. ORIGINAL RELATIONSHIP BETWEEN SELF-ESTEEM AND PSYCHOSOMATIC SYMPTOMS AND RELATIONSHIP WHICH WOULD APPEAR IF ALL SELF-ESTEEM GROUPS WERE AVERAGE IN STABILITY

	A. Original relationship						B. Relationship standardized on stability of self-picture						
Psychosomatic symptoms	Self-esteem (%)						Psychosomatic symptoms	Self-esteem (%)					
	High 0	1	2	3	4	Low 5–6		High 0	1	2	3	4	Low 5–6
0–2	69·6	58·0	46·5	40·1	28·6	19·4	0–2	66·2	57·0	47·0	42·3	28·3	18·7
3–4	19·5	26·0	28·2	33·6	31·4	31·0	3–4	21·2	25·8	27·9	32·7	34·0	31·0
5–10	10·9	16·1	25·3	26·3	40·0	49·7	5–10	12·6	17·2	25·0	25·0	37·7	50·3
Total (%)	100·0	100·0	100·0	100·0	100·0	100·0	Total (%)	100·0	100·0	100·0	100·0	100·0	100·0
Number	(477)	(796)	(724)	(456)	(245)	(155)	Number	(477)	(796)	(724)	(456)	(245)	(155)

*Standardization has been widely used in demographic and public health research to "control on" or "hold constant" certain population characteristics when comparing group rates. The method involves determining the "theoretic rates" which would appear if the distribution of these population characteristics were the same in each group as in some standard population. The standard population used in the present study is the total sample. A clear exposition of standardization procedure appears in HAGOOD[13]. A rationale for applying this method to attitude research, as well as a simplified method for calculating standardizations, appears in the author's unpublished paper *Test Factor Standardization as a Method of Interpretation.*

VOL. 1 1962/

than those with the lowest self-esteem to have few psychosomatic symptoms. If both groups were equally stable, however, the difference would be 47·5 per cent. These data would suggest, then, that stability is a "contributory factor" in accounting for the relationship between self-esteem and anxiety, although it does not appear to be a very powerful factor.

But why should people with low self-esteem tend to have more unstable self-pictures? It seems reasonable to assume that one way the person with low self-esteem would seek to deal with his problem would be to retreat into the world of fantasy, daydreaming, and imagination. Here, unencumbered by the cruel restrictions of reality, he can dream of being all great things, achieving all great victories, mastering all difficult situations. He creates, in Horney's terms, an "idealized image".*

There are at least two reasons why this may produce an unstable self-picture. The first is that the more the individual focuses his thoughts on what he would like to be, the less certain he becomes as to what he is. The distinction between his idealized image and his actual image becomes blurred in his mind. Shifting back and forth between the two, his self-conception is likely to be unstable and uncertain.

The second possible reason for such instability is the fact that, especially in adolescence, the idealized image may be constantly changing. This is probably a large component of the state which ERIKSON[14] has termed "identity diffusion", and which he finds so closely linked to anxiety. In other words, not only may the adolescent shift constantly between thinking of himself as his idealized image and his real self-picture, but he may also shift in the kind of self he would like to be. It is for these reasons that one might expect a retreat into the realm of imagination to produce an unstable or uncertain self-picture.

In order to test the general hypothesis that people with low self-esteem have more unstable images because they live more in the realm of imagination, it would be necessary to proceed as above. In other words, we would have to show that self-esteem is related to tendency to live in imagination, that tendency to live in imagination is related to instability of self-picture, that self-esteem is related to stability, and that if the factor of imagination were controlled, people with low self-esteem would not be so unstable. And the data show, in fact, that all four assumptions are true. It would thus appear that one reason people with low self-esteem have more shifting and unstable self-pictures is their tendency to retreat into the world of imagination. It may be for this reason that low self-esteem is so often considered *shaky* self-esteem.

The "presenting self"

Another factor which may contribute to the association between self-esteem and anxiety is the tendency for people with low self-esteem to present a false front or face to the world.

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*It should be noted that this conception is somewhat at odds with HORNEY's view of the origin of the idealized image. In her opinion, the idealized image arises in response to anxiety; the individual seeks to gain strength by raising himself above others in his imagination. In the present view, it is suggested that the idealized image arises in response to an unendurable state of self-contempt. It seems reasonable to assume that if an individual holds a picture of himself which he considers undesirable, then he will, in his imagination, create a picture of himself which is desirable. It is unlikely that the anxious person would seek to raise himself above others if he really considered himself to be a worthy, highly adequate person. On the other hand, it is understandable that he should want to raise himself above others if he actually considered himself below them, that he should create in his imagination a worthy person if, in the cold light of reality, he considered himself unworthy.

Like the withdrawal into the world of imagination, it may be considered a "coping mechanism" for overcoming one's low self-estimate. But while the retreat into imagination seeks to overcome a picture of worthlessness by creating an imaginary picture that one is worthy, the mechanism of the "presenting self" seeks to overcome the feeling of worthlessness by convincing others — the outside world — that one is worthy. Both mechanisms, it will be seen, only aggravate the original conditions and render the consequences more noxious.

Goffman has observed that it is characteristic of social life that it consists of a series of "social selves" or "presenting selves" which people set forth to one another. GOFFMAN[15] tends to associate these presenting selves with social roles or to relate them to instrumental purposes largely in the economic or prestige arenas. But the development of such a presenting self may also be motivated by the desire to gain the approval of others.

Our respondents were asked to agree or disagree with the following statements: "I often find myself 'putting on an act' to impress people" and "I tend to put up a 'front' to people". In each case, the lower the self-esteem, the more likely is the respondent to agree with the statement. If the responses to both questions are combined, it is found that people with low self-esteem are nearly six times as likely as those with high self-esteem to agree with both statements. It seems clear that the person who accepts himself feels less need to present a false front to the outside world.

VOL.
1
1962/

TABLE 6. SELF-ESTEEM AND TENDENCY TO PRESENT FACADE TO OTHERS

Agreement with two statements reflecting presentation of facade	Self-esteem						
	High 0	1	2	3	4	5	Low 6
Agree with both (%)	6	11	14	21	26	34	34
Agree with one	14	18	22	21	23	23	26
Agree with neither	80	71	64	58	50	42	39
Total (%)	100	100	100	100	100	100	100
Number	(484)	(816)	(725)	(451)	(246)	(120)	(38)

What is anxiety-provoking about the presentation of a facade? At least two factors may be suggested. The first is that putting on an act tends to be a strain. To act cheerful when one is sad, sympathetic when one is indifferent, friendly when one is hostile, courageous when one is timid — all this by sheer force of will and self-control — can hardly be other than a constant strain. The second source of tension lies in the possibility that one will make a false step, reveal some inconsistency, let the guise slip. Hence, the strain of maintaining the pose combined with the threat of being exposed might well produce a response of almost chronic anxiety. Table 7 indicates that respondents who say they present a facade to the world are more likely to report psychosomatic symptoms.

Since people with low self-esteem are more likely to present a false front to others and since people who present a false front manifest more symptoms of anxiety, we might assume that one reason people with low self-esteem show more anxiety is because of their tendency to present a false front.

The data appear to be in accord with this interpretation. The data indicate that if people who vary in self-esteem did not differ in their tendency to put up a front to others — if they were all average in this regard — then the relationship of self-esteem to psychosomatic symptoms of anxiety would weaken somewhat. Specifically, 70·2 per cent of those with the highest self-esteem have fewer than three psychosomatic symptoms; if these people were as likely as those with low self-esteem to put on an act with others, however, only 63·7 per cent would have fewer than three psychosomatic symptoms — a decrease of 6·5 per cent. We may thus infer that one reason people with high self-esteem have fewer anxiety symptoms is that few of them feel impelled to present a false front to the world.

OL.
1
62/63

Table 7. The "presenting self" and psychosomatic symptoms

Number of psychosomatic symptoms	Statements reflecting presentation of facade		
	Agreed with both	Agreed with one	Agreed with neither
0–2 (%)	36	46	54
3–4	27	29	27
5–10	35	25	19
Total (%)	100	100	100
Number	(445)	(565)	(1937)

Threats to self-esteem

In light of the widely accepted assumption that the sentiment of self-regard is so important to the emotional life of the individual, it can be assumed that negative self-opinions are rarely accepted with equanimity, but are, on the contrary, felt to produce uncomfortable, depressing, distressing emotional reactions. Hence, we would expect the person with low self-esteem to be inordinately sensitive to any evidence in the experience of his daily life which testified to his inadequacy, incompetence, or worthlessness. To use Horney's[2] felicitous term, they are highly *vulnerable*.

One major expression of an individual's vulnerability is his sensitivity to criticism. A Guttman scale was developed to rank people along this dimension*, and the scores were related to self-esteem. Table 8 shows that as self-esteem declines, the proportion claiming to be highly sensitive to the challenge or attacks of other people rises sharply and with

*The reproducibility of this scale was 99 per cent and its scalability was 95 per cent. It consisted of responses to the following items: (1) "Criticism or scolding hurts me terribly." (2) "How disturbed do you feel when anyone laughs at you or blames you for something you have done wrong?" and (3) "How sensitive are you to criticism?"

almost perfect uniformity. The individual's attitude toward himself is clearly related to the degree to which he is hurt, bothered, disturbed, distressed, frightened, etc., when challenged or attacked by others.

TABLE 8. SELF-ESTEEM AND SENSITIVITY TO CRITICISM OR ATTACK

"Sensitivity to criticism"	Self-esteem						
	High 0	1	2	3	4	5	Low 6
Highly sensitive (2–3%)	26	32	39	46	60	53	68
Not sensitive (0–1)	74	68	61	55	40	47	33
Total (%)	100	100	100	100	100	100	100
Number	(469)	(781)	(709)	(438)	(233)	(114)	(37)

Even implicit criticism may provoke anxiety in the person afflicted with self-contempt. For example, the respondents were asked: "How much does it bother you to find that someone has a poor opinion of you?" The data show that people with low self-esteem are much more likely than others to be disturbed by such negative evaluations.

It is not only interpersonal criticism, however, that is threatening and dangerous to the person with low self-esteem; it is also the implied criticism involved in failure at any task. One indication that people with low self-esteem are more disturbed at any evidence of incompetency or inadequacy, interpersonal or otherwise, appears in the responses to the question: "How do you feel when you do badly at something you have tried to do?" The results indicate that whereas only one-fourth of those with the highest self-esteem said they were "deeply disturbed", this answer was given by five out of every eight of those with extremely low self-esteem.

Similarly, the respondents were asked to agree or disagree with the statement: "I am deeply disturbed when I become aware of some fault or inadequacy in myself". In view of the fact that adolescents tend to be inordinately sensitive about themselves, it is not surprising to find that the majority of students agree with this statement. Nevertheless, the results show a clear and fairly regular relationship between a decline in self-esteem and a sense of disturbance at evidence of inadequacy.

People who feel inadequate, then, tend to feel more threatened by criticism or possible failure. The question now becomes: Are people who feel threatened more likely to experience symptoms of anxiety? Table 9 indicates that they are. Three-fifths of the highly sensitive students manifested a large number of psychosomatic symptoms compared with only one-fifth of those who were not sensitive to criticism. Similarly, those who were bothered by the negative opinions of others and who were disturbed at failure or the awareness of inadequacies in themselves tended to experience more psychosomatic symptoms.

If the anxiety of low self-esteem people is due in part to their greater vulnerability, then it would follow that if they were not so vulnerable, they would not experience so many

VOL. 1 1962

symptoms of anxiety, and Table 10 shows that this is so. If we make all self-esteem groups equal to the average on sensitivity to criticism, then the original difference of 36·5 per cent between the two groups would decrease to 31·3 per cent.

TABLE 9. SENSITIVITY TO CRITICISM AND PSYCHOSOMATIC SYMPTOMS

Number of psychosomatic symptoms	"Sensitivity to criticism" score			
	Not sensitive 0	1	2	Highly sensitive 3
2 or fewer (%)	68	56	40	27
3	12	12	18	14
4 or more	21	29	41	60
Total (%)	100	100	100	100
Number	(306)	(1446)	(782)	(311)

OL.
1
62/63

Feelings of isolation

The adolescent afflicted with pangs of self-contempt, we have noted, may develop at least two solutions to the problem of feelings of worthlessness: (1) he may retreat into the world of imagination where he can dream of himself as worthy, and (2) he may put up a false front to others to convince them that he is worthy. But as is so often the case with neurotic solutions, they may generate consequences more devastating than those they were designed to alleviate. One of these consequences would appear to be the development of feelings of isolation.

TABLE 10. ORIGINAL RELATIONSHIP BETWEEN SELF-ESTEEM AND PSYCHOSOMATIC SYMPTOMS AND RELATIONSHIP WHICH WOULD APPEAR IF ALL SELF-ESTEEM GROUPS WERE AVERAGE IN SENSITIVITY TO CRITICISM

A. Original relationship				B. Relationship standardized on sensitivity to criticism			
Psychosomatic symptoms	Self-esteem			Psychosomatic symptoms	Self-esteem		
	High 0–1	2–3	Low 4–6		High 0–1	2–3	Low 4–6
0–2 (%)	62·0	43·6	25·5	0–2 (%)	60·4	44·3	29·1
3–4	24·1	30·5	31·9	3–4	24·5	30·2	33·3
5–10	13·9	26·0	42·6	5–10	15·1	25·5	37·6
Total (%)	100·0	100·0	100·0	Total (%)	100·0	100·0	100·0
Number	(1229)	(1129)	(376)	Number	(1229)	(1129)	(376)

Both these factors — the private world of daydreaming and the public pose — tend to separate the person with low self-esteem from others. He cannot share himself with others fully, freely, and spontaneously. For these reasons we would expect such people to experience a fundamental feeling of loneliness.

Our respondents were asked: "Do you think most people know the kind of person you really are, or do you feel that most people do not know what really goes on underneath?" Table 11 indicates that slightly over one out of every three respondents with the highest self-esteem felt that others did not understand what they were really like underneath whereas this was true of fully five out of six people with the least self-esteem. With perfect regularity, a decreasing level of self-esteem is accompanied by an increasing proportion who feel misunderstood by others.

TABLE 11. SELF-ESTEEM AND BELIEF THAT OTHERS KNOW HOW ONE REALLY FEELS

"Do you think most people know the kind of person you really are, or do you feel that most people do not know what really goes on underneath?"	Self-esteem						
	High 0	1	2	3	4	5	Low 6
Most do not know what goes on underneath (%)	36	50	54	64	73	75	84
Most know the kind of person I really am	64	50	46	36	27	25	16
Total (%)	100	100	100	100	100	100	100
Number	(506)	(858)	(781)	(498)	(265)	(122)	(37)

It is no wonder, then, that these people come to be afflicted with a haunting sense of isolation and loneliness. "Would you say that you tend to be a lonely person?" the respondents were asked. Without exception, we find, the lower the individual's level of self-esteem, the more likely is he to be afflicted with pangs of loneliness. Only 35 per cent of those with the least self-esteem said that they were "not lonely," compared with fully 87 per cent of those possessing the highest self-esteem level.

TABLE 12. SELF-ESTEEM AND LONELINESS

"Would you say that you tend to be a lonely person?"	Self-esteem						
	High 0	1	2	3	4	5	Low 6
Very lonely (%)	1	2	3	5	8	20	22
Fairly lonely	13	19	26	35	42	37	43
Not lonely	87	79	72	60	50	43	35
Total (%)	100	100	100	100	100	100	100
Number	(520)	(878)	(797)	(505)	(271)	(125)	(37)

The feeling of loneliness is, then, not just a matter of being physically alone. A person is lonely who cannot make contact with others, communicate with them, get through to them, share feelings, ideas, and enthusiasms with them; and these are things the person with low self-esteem has difficulty in doing because of his involvement in his private world of imagination and his public pose.

Given the fact that low self-esteem may contribute to a feeling of isolation, the question may be raised: Why should feelings of isolation be associated with anxiety? We would suggest that the person who stands alone lacks social support; thus, he is more likely to feel threatened by the powerful sea of forces which surround him. He can never share himself with another completely and he can never feel the strength and reassurance which comes from such sharing and support. Hence, threats, dangers, or problems which others can work out with friends or relatives must be faced by him alone, and are therefore felt to be inordinately dangerous and anxiety-provoking.

OL.
1
62/63

Table 13 shows that people who feel lonely and isolated do indeed manifest more physiological symptoms of anxiety. Similarly, people who feel misunderstood are more likely to manifest these physiological symptoms of anxiety. Students who felt that others knew what they were really like underneath had fewer psychosomatic symptoms than those who felt that their inner lives were closed to others.

Table 13. Feelings of loneliness and psychosomatic symptoms

Number of psychosomatic symptoms	"Would you say that you tend to be a lonely person?"		
	Very lonely	Fairly lonely	Not lonely
0–2 (%)	21	38	56
3–4	32	31	26
5–10	47	31	18
Total (%)	100	100	100
Number	(124)	(818)	(2280)

In light of these results, we would expect that if feelings of isolation were controlled, the relationship between self-esteem and anxiety would decrease. Table 14 shows that this is so. Whereas those with high self-esteem are 36·3 per cent more likely than those with low self-esteem to have few psychosomatic symptoms, the data show that if both groups did not differ in feelings of isolation, the difference would be reduced to 31·3 per cent.

Joint effect

In the foregoing discussion, four factors which may contribute to the association between self-esteem and anxiety have been suggested; none of these factors accounts for the relationship completely, but each appears to contribute to it in part. Due to the limited number of cases, it is not possible to control on all four factors simultaneously, but we have been able to control on three of them. Table 15a shows the original relationship between self-esteem

TABLE 14. ORIGINAL RELATIONSHIP BETWEEN SELF-ESTEEM AND PSYCHOSOMATIC SYMPTOMS AND RELATIONSHIP STANDARDIZED ON FEELINGS OF LONELINESS

A. Original relationship				B. Relationship standardized on feelings of loneliness			
Number of psychosomatic symptoms	Self-esteem			Number of psychosomatic symptoms	Self-esteem		
	High 0–1	2–3	Low 4–6		High 0–1	2–3	Low 4–6
0–2 (%)	62·4	44·2	26·1	0–2 (%)	60·5	44·7	29·2
3–4	23·5	30·1	31·5	3–4	24·0	29·8	32·0
5–10	14·0	25·7	42·4	5–10	15·5	25·5	38·8
Total (%)	100·0	100·0	100·0	Total (%)	100·0	100·0	100·0
Number	(1374)	(1279)	(425)	Number	(1374)	(1279)	(425)

and psychosomatic symptoms and Table 15B shows this relationship when it is standardized simultaneously on feelings of isolation, sensitivity to criticism, and instability of self-image. It will be seen that the original difference of 36·8 per cent decreases to 26·7 per cent. These three factors considered jointly, then, make a fairly substantial contribution to the original relationship, although they by no means account for it completely.

TABLE 15. SELF-ESTEEM AND PSYCHOSOMATIC SYMPTOMS: (A) ORIGINAL RELATIONSHIP; (B) RELATIONSHIP STANDARDIZED ON THREE TEST FACTORS

A. Original relationship				B. Standardized relationship			
Psychosomatic symptoms	Self-esteem			Psychosomatic symptoms	Self-esteem		
	High (%)	Medium (%)	Low (%)		High (%)	Medium (%)	Low (%)
0–2	69·5	52·3	32·7	0–2	65·4	51·3	38·7
3–4	19·9	27·3	32·7	3–4	21·3	27·4	32·9
5–10	10·6	20·4	34·6	5–10	13·3	21·7	28·9
Total (%)	100·0	100·0	100·0	Total (%)	100·0	100·0	100·0
Number	(452)	(1420)	(789)	Number	(452)	(1420)	(789)

To say that the joint impact of the several "explanatory" factors cited here is stronger than the impact of each considered individually is not to deny that each explanatory variable may not to some extent be contaminated by the others. For example, if we show that sensitivity to criticism partly accounts for the relationship of self-esteem to psychosomatic symptoms, we cannot be certain that sensitivity to criticism may not be reflecting at the

VOL. 1 1962/

same time, say, instability of self-image or feelings of isolation. We have, at least, guarded against this danger to the following extent. Every explanatory variable considered in this paper has been related to psychosomatic symptoms controlling separately on every other variable, including self-esteem. It turns out that each of these factors is related to psychosomatic symptoms independently of the others.*

4. SUMMARY AND CONCLUSIONS

The aim of this study has been to investigate the relationship between self-esteem and anxiety and to suggest certain reasons why low self-esteem may generate anxiety. Questionnaires were administered to all juniors and seniors in a random sample of ten high schools in New York State; three separate but overlapping questionnaires were administered alternately to 5,077 students. *Self-esteem* was measured by means of a ten-item Guttman scale possessing a satisfactory level of reproducibility and scalability. *Anxiety* was indexed by reports of "psychosomatic symptoms" which, in other research, had proved to discriminate powerfully between diagnosed neurotics and a random sample of normal people. The results indicate a clear inverse relationship between self-esteem level and anxiety level.

Four factors associated with self-esteem which might be expected to contribute to anxiety were suggested: the instability of the self-image, the presenting self, threats to self-esteem, and feelings of isolation. Self-esteem was found to be related to each of these factors; each of these factors was related to psychosomatic symptoms of anxiety; and when each of these factors was controlled, the relationship of self-esteem to anxiety decreased to some degree. This would suggest that these four factors contributed in some measure to the relationship between self-esteem and anxiety.

One of the central purposes of this report has been to specify certain methodological requirements which must be met if we are to make a confident statement that self-esteem generates anxiety for the reasons specified. It is hoped that broad-scale systematic data dealing primarily with conscious factors, such as those presented here, may prove to be a useful supplement to the more established intensive clinical procedures and the more rigorously controlled experimental methods in establishing dependable knowledge about the nature of the neurotic process.

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*Space limitations prevent us from presenting the thirty-two tables upon which this statement is based.

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VOL
1
1962

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BINOCULAR RIVALRY OF GENDER-SIGNIFICANT PICTURES IN A STEREOSCOPE*

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VOL.
1
962/63

INTRODUCTION

WITHIN the broad context of perception and interpersonal relations (CANTRIL[1]), there is appearing in the literature an increasing amount of experimental work on binocular rivalry with the use of a stereoscope. ENGEL[2] noted that male subjects presented with an inverted and an upright male profile, one in each side of a stereoscope, reported seeing only the upright stimulus. BAGBY[3] found that Mexicans simultaneously presented with typical Mexican and American scenes reported seeing more Mexican scenes than a corresponding group of Americans who contrarily saw more of the American scenes. DAVIS[4] demonstrated different patterns of responses between a normal and a schizophrenic group when conflicting visual stimuli such as a knife fight and a baseball game were simultaneously presented. BELOFF and BELOFF[5] had subjects rate for attractiveness a composite face which resulted from the separate presentation in each half of a stereoscope of their own face and that of a stranger against a composite resulting from the presentation of two faces other than their own. UNGER and IMBODEN[6] found differences between female post-operative rhinoplasty patients and nonrhinoplasty patients simultaneously presented with female pre- and post-operative rhinoplasty profiles. VAN DE CASTLE[7] simultaneously presented conflicting words in a stereoscope and found a correlation between the personality types of his subjects and the types of words that assumed perceptual dominance.

During the past few years we have been studying prepubertal children with incongruous gender role — specifically young boys who were assuming many of the behavioral characteristics of girls[8,9]. With earlier stereoscopic studies as a stimulus, we became interested in the possibility of a perceptual test that might be relatively specific for psycho-sexual identity.

HYPOTHESIS

In the experiment here reported, the following hypothesis was investigated. When rival pictures, one of masculine, the other of feminine significance or representation, are simultaneously presented, one to each eye, through a stereoscope, young adult men and women will differ regarding which picture assumes perceptual dominance.

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EXPERIMENTAL MATERIALS

A stereoscopic apparatus to accommodate 2 in. × 2 in. cards was constructed by adapting an ophthalmologic telebinocular.* The stereoscope was divided into a right and left light-proof compartment by a central partition. Eye pieces were adjustable to accommodate for esophoria and exophoria and for differing interocular distances of viewers. A manually operated, push-button switch controlled the length of time slides were illuminated. Intensity of illumination was separately controlled by a rheostat for each compartment.

The visual stimuli were twenty-six matched pairs of 2 in. × 2 in. cards. Each card contained an illustration in black, white and grey, such that one member of each pair illustrated something of masculine significance and the other something of feminine significance. There were five groups of cards as shown in Table 1.

TABLE 1. VARIETIES OF MATCHED PAIRS OF 2″ × 2″ CARDS

	Group A. Cards without human figures
Subgroup I: (6 pairs)	Objects, generally identifiable with femaleness, vs. objects generally identifiable with maleness, e.g., man's shoe vs. woman's shoe baseball vs. ball of yarn
	Group B. Cards with human figures
Subgroup II: (4 pairs)	Scenes, identifiable *ordinarily* with one sex, drawn with the congruous sex on one card and the incongruous sex on the other, e.g., male at stove cooking vs. female at stove cooking male painting house vs. female painting house
Subgroup III: (7 pairs)	Scenes, identifiable *exclusively* with one sex, drawn with the congruous sex on one card and the incongruous sex on the other, e.g., male breast feeding infant vs. female breast feeding infant male entering "ladies" room vs. female entering "ladies" room
Subgroup IV: (6 pairs)	Male vs. female figures, alone, or in activities consistent with their gender, e.g., male shaving vs. female powdering face male profile vs. female profile
Subgroup V: (3 pairs)	Romantic and love scenes with and without gender incongruous partners, e.g., male profile at penis vs. female profile at penis male kissing male vs. female kissing female

EXPERIMENTAL PROCEDURE

The phenomenon of binocular rivalry in the present type of experiment may be influenced by the content of the images exposed; by relative differences of configuration, size, shading or other physical properties of the two images; by the amount of illumination on each image; or by the natural dominance of the subject's right or left eye.

*One variety of this instrument is manufactured by the Keystone View Company, Meadville, Pennsylvania.

VOL. 1 1962/

An attempt was made to keep constant the variability of the physical properties of the two images by having representations so drawn that ambiguity was limited to the critical parts of figures of the drawing in each pair. The rest of the representation in each pair was made to be as nearly alike as possible (Fig. 1).

FIG. 1. Rivalrous pairs of gender-significant pictures. All pairs belong to Group B (Table 1). Subgroups II (top left), III (top and bottom right) and IV (bottom left) are represented.

It is difficult to obtain great precision in holding constant the factor of eye dominance, but it is imperative not to disregard the matter. DURAND and GOULD[10] drew critical attention to the problem as early as 1910. UPDEGRAFF[11] demonstrated that there is but a moderate degree of relationship between motor-eyedness and left-handedness. WASHBURN, FAISON and SCOTT[12] showed that preference in sighting, for example in using a gun, is not closely related to the dominant eye in tests of retinal rivalry. JASPER and RANEY[13] differentiated ocular or eye-muscle dominance from dominance of the visual fields and central visual mechanism, and developed a phi test that gave confirmatory evidence when the results were compared with other tests of dominance. BUXTON and CROSLAND[14] showed that there is poor reliability between varying methods of determining eye preference. Very recently, however, CROVITZ[15] reopened the issue with the finding of an association between sighting-dominance and acuity-dominance, plus the fact that most individuals tested showed acuity-dominance of the left eye.

The physiology of eye dominance is largely unknown. BÁRÁNY and HALLDÉN[16] did a study of phasic inhibition of the light reflex of the pupil during retinal rivalry, and reached the conclusion that, during rivalry, a phasic inhibition takes place peripherally, probably in the retinae themselves.

In the present study, in order to overcome limitations pointed out by the above authors, eye dominance of our subjects was ascertained under conditions closely approximating those

of the experimental situation. A pair of cards was introduced into the stereoscope with the degree of illumination in each half of the apparatus equal, and the subject was asked to report what he saw. Then the pair of cards was reversed in position so that each member of a card pair was being viewed by the alternate eye. The subject was again asked to report what he saw. Relative illumination of each compartment of the stereoscope was then adjusted by means of one of the rheostats, to ensure dominance of one eye.

As an alternative to ensuring dominance of one eye, the goal of light adjustment could have been to try to eliminate dominance in all subjects by giving the dominant eye less light (very few people favor both eyes equally). This alternative was rejected in planning the experiment. It is difficult to guarantee that perfect lack of dominance has been attained. Moreover, positive results obtained in the face of enforced eye dominance would be far more convincing.

To make sure that every subject had one dominant eye, the few subjects without native eye dominance were given increased illumination on one side; those with extreme native dominance of one eye had the illumination on that side slightly reduced, because extreme dominance precluded seeing anything at all out of the nondominant eye. In each case the end point of the test trial was reached when the picture before a subject's dominant eye was seen during most of the presentation and the picture before the nondominant eye was seen for fleeting periods. The rheostats remained fixed at this same degree of illumination for the remainder of the experiment. There was no time limit on exposures during the preliminary trials but, during the test proper, exposures were limited to 10 sec.

To ensure that drawings on each card pair would be properly superimposed and centered for each subject, a test pair of cards consisting of a row of six vertical dots on one card and six horizontal dots on the other was introduced into the stereoscope. The subject was told to adjust the eye pieces until the rows of dots superimposed to present a symmetrical "plus sign".

The series of twenty-six pairs of cards was presented twice. On the second run through, the left and right placement of the cards was reversed. Thus each picture of each pair of cards was seen in front of the dominant eye and the nondominant eye, respectively.

Members of a card pair were presented in such order that, before a given eye, the order of pictures was masculine, feminine, feminine, masculine, followed by feminine, masculine, masculine, feminine, etc. (ABBA, BAAB, ABBA, etc.). On the first presentation the pairs of cards were presented in random order. To cancel a possible sequence-learning effect, on second presentation odd-numbered card pairs were presented first, followed by even-numbered, or vice versa.

Ten seconds were allowed for viewing a pair of cards. Subjects were asked "What do you see?" "Do you see anything else?" and "Which do you see more?"

Responses to card pairs were categorized as being (1) male content-dominant, (2) female content-dominant, or (3) eye dominant.

"Male content-dominant" was recorded: (a) when the male member of a card pair was seen exclusively on both presentations, (b) when the male member of a card pair achieved dominance over the female member on both presentations, although the female member could be seen for brief periods, (c) when on one presentation only the male member was seen, and on the re-presentation both male and female members were seen with equal clarity.

VOL.
1
1962/

"Female content-dominant" was recorded when responses were the obverse of the above.

"Eye dominant" was recorded when the picture in front of the dominant eye was seen on both occasions irrespective of the content of the picture.

The fourth logical possibility, that of seeing the member of a pair in front of the non-dominant eye on both occasions irrespective of the content of the picture, was not employed. Such responses did not occur, thus giving clear evidence of the success of the method of ensuring unilateral dominance in every subject.

SUBJECTS

Male subjects numbered thirty of whom twenty-seven were medical students, and three hospital employees. The average age was 23. Female subjects numbered thirty of whom twenty-seven were student nurses, two medical students and one a physician. The average age was 22. Subjects were procured in answer to a posted bulletin calling for volunteers for a "100 per cent benign visual psychology experiment" for which they would be paid $2.00 for an hour of their time. Before participating in the experimental procedure each subject was advised that no attempt was being made to learn anything about him or her as an individual, but merely to note whether, as a whole, males and females reacted differently in this experimental situation.

OL.
1
62/63

FINDINGS

Findings were summarized in three different ways, comparisons being made in each instance for three classifications of the cards: (a) all twenty-six cards; (b) those six cards which contained objects but no human face or figure (Group A); (c) those twenty cards which contained the human face or figure (Group B).

Content-dominant responses of men and women

In Table 2 men and women are compared for the absolute number of male content-dominant responses, female content-dominant responses and for the combined total of both.

TABLE 2. MALE VS. FEMALE CONTENT-DOMINANT RESPONSES OF MEN AND WOMEN

Card group	Female content-dominant		Male content-dominant		Total content-dominant	
	Mean for 30 men	Mean for 30 women	Mean for 30 men	Mean for 30 women	Mean for 30 men	Mean for 30 women
All 26 cards	4·97	3·93	1·90	2·20	6·87	6·10
	$t=1{\cdot}06$; $p<0{\cdot}3$		$t=0{\cdot}45$; $p<0{\cdot}7$		$t=0{\cdot}89$; $p<0{\cdot}4$	
20 cards with human figures (Group B)	4·57	2·80	1·33	1·57	5·90	4·37
	$t=2{\cdot}29$; $p=0{\cdot}025$		$t=0{\cdot}53$; $p<0{\cdot}6$		$t=1{\cdot}20$; $p<0{\cdot}25$	
6 cards without human figures (Group A)	0·40	0·60	0·57	0·63	0·97	1·37
	$t=1{\cdot}00$; $p<0{\cdot}4$		$t=0{\cdot}20$; $p<1{\cdot}0$		$t=1{\cdot}43$; $p<0{\cdot}2$	

No difference between men and women subjects was found for the combined total of male content-dominant and female content-dominant responses, nor in the absolute number of male content-dominant responses taken separately. In the case of female content-dominant responses, men made significantly higher scores ($p = 0{\cdot}025$) than women on those card pairs which contained human faces or figures (Group B). There were no differences between men and women for the card pairs with only gender-significant objects (Group A).

High vs. low content-dominant responders

Each subject's scores were allocated a numerical rating as follows:

(a) A *plus* for female content-dominance,
(b) A *minus* for male content-dominance,
(c) A *zero* for eye-dominance.

Then the algebraic sum of the pluses and minuses was calculated for each subject for both groups of cards, with and without human figures, separately and combined.

For each of the three classifications of the cards, subjects (men and women separately) were ranked in order by the total number of content-dominant responses they made. The median score was used as the dividing point whereby men and women were separated into low and high content-dominant responders. This procedure produced a four-cell table, comprised of men vs. women and high vs. low responders. This table was subject to a 2×2 analysis of variance. Owing to a lack of homogeneity between the four cells, transformation of the raw scores was performed by adding two to each score to eliminate negatives, and then taking the square root of the result.

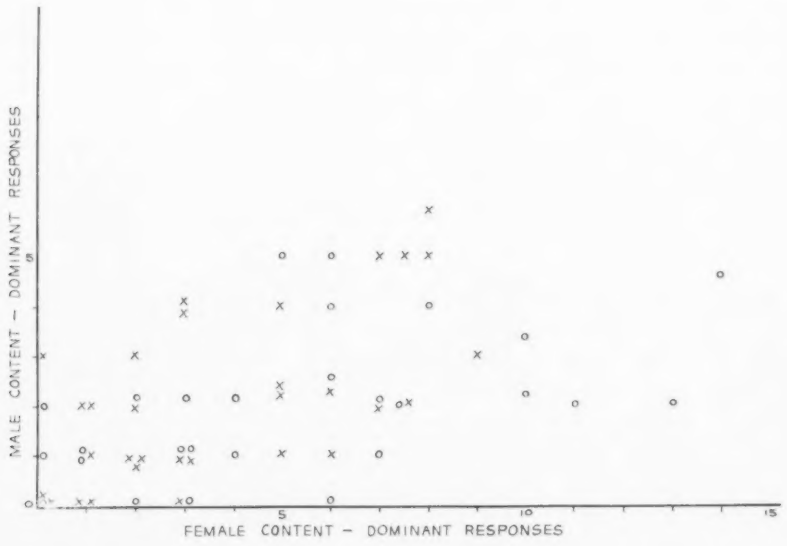

FIG. 2. Male vs. female content-dominant responses for each of 60 subjects (o = male; x = female)

Division into low and high content-dominant responders overcame to some degree the limitation of the tripartite scoring system (male content-dominant; female content-dominant; eye dominant) in which only the first two of the three possible scores were compared. This insurmountable limitation allowed a subject who gave eight female content-dominant responses and seven male content-dominant responses to achieve the same algebraic score as a subject whose ratio was two female to one male.

There was a significant difference at the 5 per cent level of confidence between men and women for the twenty card pairs with human faces or figures (Group B). The difference between men and women for the six cards with objects only (Group A) was not significant. Further, except for Group A cards (with gender-significant objects but no human figures) the high content-dominant responders of both sexes taken together scored signficantly differently from the low content-dominant responders ($p<0{\cdot}001$). This difference was due to the fact that men and women both favored female content-dominance as their content-dominant responses increased in number (see Fig. 2).

VOL.
1
962/63

Analysis of content-dominance by subgroups

Data for this analysis of variance were tabulated in the same manner as in the preceding section, except that the twenty-six card pairs were subdivided into the five subgroups of Table 1.

Significant differences ($p<0{\cdot}05$) were found only for card subgroups III and IV. In sub-III, the cards portrayed scenes identifiable exclusively with one sex, drawn with (a) the congruous and (b) the incongruous sex substituted and in subgroup IV, male children or adults vs. female children or adults were portrayed alone, and in activities consistent with their gender.

The differences noted between men and women in the preceding section were, thus, largely attributable to the responses to card subgroups III and IV. Any special significance these two card subgroups may have is not clear.

DISCUSSION

The present experiment was designed to pay more attention than its predecessors to regulating eye dominance, adjusting for binocular accommodation, and equalizing stimuli as much as possible for mass, contour and shading. This extra procedural rigor may account for the fact that the effects of attitude on resolution of binocular rivalry were not striking in the present study as in those reported by others.

An alternative explanation may be that gender-significant pictures are not a good medium for detecting male versus female differences of attitude on resolution of binocular rivalry. To illustrate: a cover girl picture may be content-dominant to a male viewer because it is erotically arousing. The same picture may be content-dominant to a woman viewer also, but because she projects herself into the seductive role of the cover girl. Binocular resolution would thus be the same for the two sexes, even though the underlying attitudes were different.

The sex difference obtained in the present experiment was not a difference in the masculinity or femininity of pictorial content dominance of men versus women viewers. It was

a quantitative difference in which men and women both favored female content-dominance, but with men obtaining higher scores than women. On the basis of this evidence, the technique proves disappointing as a method for investigating gender role and identity, since it shows simply a trend toward quantitative without also typological, qualitative difference between the sexes.

In addition, some people are high, some low content-dominant responders, irrespective of sex. Possibly this difference in perceptual type may prove to be related to personality type. In general, however, the findings of the present experiment point to a need for greater methodological caution than formerly in relating personality and attitude to perception in the resolution of binocular rivalry.

CONCLUSION

When rival pictures are viewed simultaneously in pairs in a stereoscope, the picture that assumes perceptual dominance is not always the one that is before the dominant eye. In some instances, and in some people more than others, some process is at work which causes the picture before the nondominant eye to assume perceptual dominance. This process may pertain partly to factors of mass, contour and shading in the picture and partly to the content-meaning of the picture. When the two pictures contain human figures, one of one sex, one of the other, against backgrounds of similar shape and shading, there is a tendency for the responses of men and women subjects to differ, namely, more men than women blot out the male picture, even when it is before the dominant eye, in favor of the female picture. It will require further experimentation to delineate the relative importance of these various factors that influence the resolution of stereoscopic rivalry, and to learn why there are people in whom eye dominance is overcome frequently and those in whom it is overcome seldom.

VOL.
1
1962/

SUMMARY

Twenty-six pairs of 2 in. × 2 in. illustrations were shown in a stereoscope. Each pair was matched for size, shading and contour of the designs, but one design was of masculine, the other of feminine significance. Intensity of illumination was regulated separately in each lateral compartment of the stereoscope in such a way as to guarantee that each subject had the vision of one eye dominant over the other. There were thirty men and thirty women subjects. The experiment was designed to see if the nondominant eye would sometimes take precedence over the dominant; if so, whether the gender-significant content of the rival pictures was an important factor; and whether men differed from women in the precedence given to the masculine or feminine content of pictures.

There was no overall significant difference between men and women in total number of content-dominant responses, nor of male content-dominant responses. But men got more female content-dominant responses ($p = 0{\cdot}025$ by one method of scoring and 0·05 by another) than women on the twenty card pairs that portrayed human faces or figures — i.e., they saw the feminine portrayal in front of the nondominant eye to the exclusion of the masculine portrayal in front of the other eye more often than the women did. High content-dominant responders of both sexes differed from low ($p = 0{\cdot}001$) and favored female content-dominance as their total content-dominance score increased.

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OL.
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62/63

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PLASMA CORTISOL IN DEPRESSIVE ILLNESS

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VOL.
1
1962/

INTRODUCTION

IN RECENT years the activity of the adrenal cortex has been intensively studied in human subjects undergoing emotional disturbance. Earlier investigations were concerned with the assessment of indirect indices such as eosinophil levels in the peripheral blood or with the measurement of urinary metabolites of adrenocortical hormones. More recent studies have been concerned with the plasma concentration of cortisol, as this appears to be a more direct index of adrenocortical activity. It has been shown in several centres that emotional turmoil or distress is accompanied by a raised plasma cortisol level. In groups of such subjects the mean value, assayed by the technique of NELSON and SAMUELS[1] has consistently been found to be about 18–20μg compared with a normal mean value of 12–14μg/100 ml. This is so when the emotional disturbance is a direct response to a distressing life situation, as in relatives accompanying casualties to hospital[2] or in patients awaiting major surgery[3], and also when it is part of a psychiatric illness such as acute schizophrenia[2] or severe anxiety[4]. The anxious patient in particular has been very thoroughly studied[5].

Depressive illness is well suited for the study of adrenocortical activity in relation to emotional distress since it is a common illness and since most depressed patients recover or improve within a comparatively short time. Two papers from the Michael Reese hospital have dealt with plasma cortisol levels in depression[6,7]. The authors found significantly higher mean values in depressed patients than in normal controls (19·5μg vs. 12·3μg/100 ml). The more emotional distress the patient was undergoing, the higher was the cortisol level. Subsequent testing revealed that the levels generally fell, although a few patients who had received electroconvulsive therapy showed increasing levels after hospital admission. It was suggested that the latter patients, whose depression had been severe and prolonged, might have been suffering from adrenal exhaustion at the time of admission. None of the patients, however, was tested for longer than 2 weeks. It seemed to us that further information might be gained from repeated estimations of plasma cortisol for several weeks, until the patient had recovered or was at least ready for discharge.

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CASE MATERIAL AND METHODS

The investigation was conducted on seventeen patients, eleven male and six female. One patient was seen during two separate admissions (cases 6 and 18) so that there were eighteen periods of observation in all. The age range was 14–70. The patients were considered by their physicians to be suffering from moderate or severe depressive illnesses of a typical nature, and in each case it was believed that the illness was a primary affective disorder. The syptoms in every case included persistent depression of mood with at least feelings of unworthiness or self-blame and often frank delusions of guilt. Other universal features were impairment of concentration, lack of initiative, interest and energy, difficulty in sleeping and decrease in appetite. Alteration in motor activity was usual, either in the direction of retardation or agitation. While precipitating factors were evident in a minority of cases, the clinical features were those of so-called endogenous depression. No attempt was made to differentiate involutional melancholia from depression in general. Eight patients had had previous depressive illnesses. The diagnosis was later called into question in case 14, who was thought to be probably schizophrenic. One patient showed evidence of chronic, mild organic impairment (case 2) and another was considerably malnourished (case 13). Otherwise the patients were in reasonably good physical health. Case 3 was a 14-year-old cyclothymic girl who suffered from phases of retarded depression lasting about a fortnight followed by mild elation for three to four weeks.

No patient was receiving anticepressive treatment when the investigation was begun, although several had taken antidepressive drugs without lasting benefit before admission. All except case 3 received small amounts of barbiturate hypnotics because of insomnia; the usual dose was 200–400 mg of sodium amylobarbitone. Later treatment consisted of electroconvulsive treatment (ECT) in twelve cases and an antidepressive drug (Imipramine) in five (of whom two had ECT as well). The dosage of imipramine was 25 to 50 mg thrice daily. Three patients (3, 16 and 18) received no 'specific' antidepressive treatment. On two occasions a patient left hospital prematurely while still obviously depressed, despite some improvement (cases 2 and 18); the remaining sixteen were considered to be recovered or to be suffering from only mild residual symptoms at the time of discharge.

Plasma cortisol was measured at weekly intervals until the patient was discharged. The first estimation was not carried out until at least a week after admission (except in cases 7 and 10 when early treatment was proposed) since the experience of admission to hospital may be an adrenocortical stimulus[8]. 25 ml of venous blood were drawn between 9.0 and 9.30 a.m. on the same day of each week and collected in a heparinized bottle. The plasma was separated immediately by centrifuging and was then frozen and stored. Usually several samples from one patient were analyzed together. Cortisol was measured by the method of PETERSON *et al.*[9], with the minor modifications introduced by HATFIELD and SHUSTER[10]. Each estimation was performed on duplicate 5 ml aliquots of plasma and from the duplicate results the standard deviation, calculated by the method suggested by BRAUNSBERG and JAMES[11], was approximately 1μg in the range 5–30μg per 100 ml.

After blood had been drawn one of us made an assessment of the patient's state during a brief interview, basing his judgment on the patient's appearance and behaviour and on his replies to questions about his mood and preoccupations. The same patient was always

TABLE 1. WEEKLY PLASMA CORTISOL LEVELS AND CLINICAL RATINGS

Case	Weeks 1	2	3	4	5	6	7	8	9	10	11	12
1	23·4	[d] 20·0	21·7	11·0	6·0	9·4	9·9					
	4	4	3	3	2	0	0					
2	27·0	23·6	[d] 15·2	13·7	24·8	[e] 12·7	17·3	13·3				
	4	3	3	3	3	3	3	2				
3	27·0	25·0	19·5	10·8	7·2	8·0	6·2					
	3	3	1	0	0	0	0					
4	16·0	[e] 19·0	18·0	10·4	7·4	7·0	6·0					
	3	2	2	2	1	1	0					
5	29·4	[e] 17·4	13·1	8·6	14·4	17·0	3·4	—	10·0			
	4	3	3	2	0	0	0	—	0			
6	20·0	21·5	[d] 15·6	3·4	3·5							
	3	3	1	0	0							
7	27·8	20·0	[e] 16·0	16·0	12·6							
	3	3	1	0	0							
8	17·4	34·0	[e] 15·2	7·0	5·0	10·0	4·0	—	9·0	9·5		
	4	4	3	2	2	1	0	—	0	0		
9	20·6	—	[e] —	23·4	16·0							
	3	—	—	2	0							
10	—	[e] 21·0	14·0	—	—	14·0	10·0					
	3	3	1	—	—	1	0					
11	35·0	35·0	[d] 24·3	30·0	18·0	[e] 15·0	12·0	15·2	6·6	11·0	—	11·5
	4	4	4	4	3	2	0	0	0	0	—	0
12	21·4	[e] 43·4	21·5	10·4	7·2	7·0	13·4					
	4	4	3	2	0	0	0					
13	18·4	15·8	[e] 12·2	14·2	9·6							
	4	3	2	0	0							
14	10·0	[e] 13·0	11·7	11·2	—	10·5	12·0	7·4	11·7			
	4	3	1	0	—	3	1	0	0			
15	10·4	[d] 8·8	13·0	10·0	4·8	7·4	9·6	8·0	5·0	8·3		
	2	2	2	1	1	0	0	0	0	0		
16	10·0	18·6	6·0	—	—	9·3						
	2	2	1	—	—	0						
17	15·2	—	[e] 24·4	14·0	22·0	—	—	16·5				
	3	—	1	1	1	—	—	0				
18	25·0	21·4	12·0	—	25·4	18·0						
	3	2	2	—	2	2						

In each row the upper figures represent plasma cortisol in μg per 100 ml, the lower figures are the clinical ratings of degree of depression from 0 to 4.

VOL. 1 1962

assessed by the same observer. Depression was rated on a 5 point scale as follows: 0 — no evident depression, 1 — mild blueness, 2 — significant depression, not of itself incapacitating, 3 — depression severe enough to warrant admission to hospital, 4 — severe and deep depression. The presence or absence of moderate or marked agitation or retardation was also noted. The ratings were written down at the time of observation so that the clinical measurements were independent of the subsequent chemical findings. It must be stressed that this was an assessment of the patient's clinical state at the time of venepuncture and not of his overall state during a particular week. Hence a rating of 0 means that the patient showed no evidence of depressed mood, but does not imply that he was necessarily free from all the symptoms that make up the clinical picture of depressive illness.

RESULTS

Plasma cortisol levels and clinical ratings of depression are shown in Table 1. One week elapsed between each estimation. When no chemical data were available the omission is indicated by a dash. The week during which treatment was begun is indicated in the table by 'e' in the case of ECT, 'd' in the case of drug treatment. In case 1, for example, one estimation of plasma cortisol was made before drug treatment began, and in case 7 there were two estimations before ECT was begun.

The mean of the first estimations was 20·8μg/100 ml (S.D.= 7·03), and of the last in each patient 10·8μg (S.D.= 3·74). The mean difference, 10·0μg, is highly significant: by the method of correlated means $t = 6{\cdot}105$, $p < 0{\cdot}001$. There was no overall decline after only one week; the mean of the second estimations was 22·1μg. Examples of serial estimates in individual cases are illustrated graphically in Figs. 1–3.

TABLE 2. PLASMA CORTISOL LEVELS ACCORDING TO CLINICAL RATINGS

Clinical rating	No. of estimations	Mean and standard error
4	14	26·3 ±2·36μg/100 ml
3	27	18·6 ± 0·95
2	21	13·6 ± 1·08
1	17	13·2 ± 1·47
0	39	9·5 ± 0·58

All differences in mean plasma cortisol levels (except that between clinical ratings 2 and 1) are significant at the 1% level.

In order to illustrate the relationship between hormone levels and intensity of depression Table 2 shows the mean and standard deviation of all the cortisol levels for each depressive rating from 4 to 0. It will be seen that there is a definite tendency for the plasma cortisol to vary directly with the severity of the depression. When only the first estimations are considered, however, no difference in mean cortisol level is seen in the two most severely ill groups: the mean was 22·8μg/100 ml for the eight patients with a depressive rating of 4, 21·6μg for the eight with a rating of 3, 10·2μg for the two with a rating of 2.

TABLE 3. CHANGES IN CORTISOL LEVELS AND CLINICAL RATINGS

		Clinical rating		
		Unimproved	Improved	Total
Cortisol level	Increased	16	8	24
	Unchanged	20	9	29
	Decreased	18	29	47
	Total	54	46	100

$X^2 = 8{\cdot}640$ $\quad 0{\cdot}01 < p < 0{\cdot}02$

In Table 3 the relationship between change in mental state and change in hormone levels is examined. Each depressive rating except the first is compared with that of the previous week and the patient's clinical state is classed as 'improved' if the rating is lower, 'unimproved' if it is unchanged or higher. Similarly the hormone level is compared with that of the week before and classed as showing an increase, a decrease, or no significant change. (A change of 3μg or more was taken to be significant.) It is clear that there was no consistent relationship between the weekly changes in the two variables, but the most frequent association was between psychological improvement and a decline in plasma cortisol level. A chi-square test suggests that this association is not simply a random one. To express it in a different way, a decline in cortisol level occurred on twenty-nine of the forty-six occasions when improvement had occurred, but on only eighteen of the fifty-three occasions when there had been no clinical improvement. The difference between these fractions is statistically significant ($p < 0{\cdot}01$).

Mean cortisol levels were calculated for the thirteen occasions when marked retardation was noted and for the eight when marked agitation was observed: these were 25·1 and 24·3μg/100 ml respectively. In each case the clinical rating of depression was either 4 or 3.

Table 1 gives details of only one attack of depression in case 3. In fact she was tested during three depressed phases in 16 weeks and full details are set out in Table 4, where the symbol X is used to indicate the presence of mild elation or excitement.

TABLE 4. FULL DETAILS OF WEEKLY CORTISOL LEVELS AND CLINICAL RATINGS, Case 3

Week	1	2	3	4	5	6	7	8
	27·0	25·0	19·5	10·8	7·2	8·0	6·2	19·0
	3	3	1	0	X	X	X	3
Week	9	10	11	12	13	14	15	16
	16·8	6·0	—	—	32·0	21·5	11·3	6·5
	1	0	X	X	3	2	0	X

In each row the middle figure represents plasma cortisol in μg per 100 ml. The lower figure is the clinical rating of severity of depression, on a scale from 0 to 4, with X indicating mild elation.

DISCUSSION

The mean values cited in Table 2 support the main finding of BOARD *et al.*[7], namely that depressed patients as a group have raised plasma cortisol levels, at least in the morning. Moreover, the levels fall to normal after adequate treatment. There is throughout a good correlation between hormone level and the intensity of the depression as judged clinically. The initial raised levels are unlikely to be due merely to admission to hospital or to the procedure of venepuncture and interview. All except two of the patients had been in hospital at least a week and all of them had had several interviews and at least one venepuncture since admission. That the decline in plasma cortisol level is at least in part the result of the improvement in mental state is suggested by the data of Table 3. It is hardly surprising that both increases and decreases in the cortisol level occurred in the presence of an unchanged mental state; no one would suggest that emotion is the sole determinant of plasma cortisol concentration. Moreover our assessment referred only to the clinical state at the time of interview, while the patient's overall state throughout the day or previous days may have been more closely related to his hormone level.

Group statistics, however, tell only part of the story, and it is instructive to look at the findings in each individual patient. Study of Table 1 shows that in thirteen instances

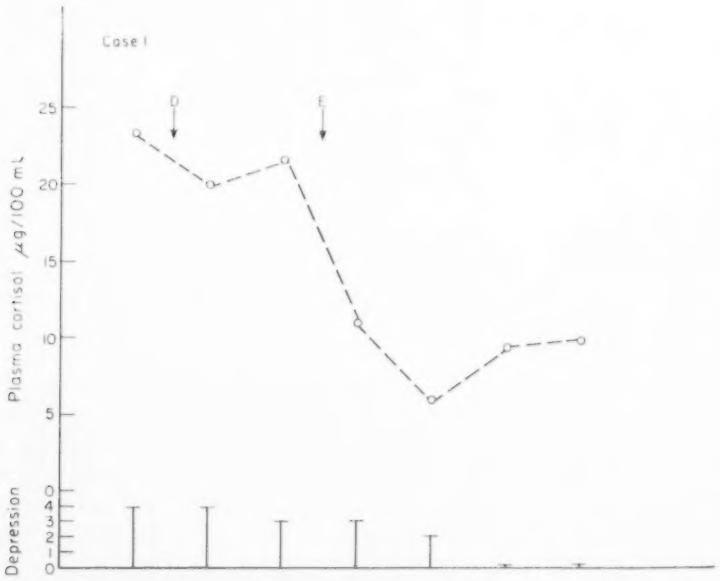

FIG. 1. Weekly plasma cortisol levels and clinical ratings of depression in case 1. A fluctuating decline in cortisol level accompanies clinical improvement.

(cases 1–13) there was a general decline in plasma cortisol, sometimes with considerable fluctuations, during the patient's stay in hospital. Examples are displayed in Figs. 1 and 2. In case 2 the fluctuating decline was accompanied by only partial psychological improve-

ment; the patient was still mildly depressed when he discharged himself. In cases 8 and 12 there was an initial considerable increase, reminiscent of the increase reported by BOARD *et al.*[7] in their group of severe depressives who received ECT. These were the only two cases of our series in which this phenomenon occurred. Both were severely depressed, but the same was true of six other patients who had a rating of 4. The sharp increase followed ECT in only one patient, and in neither of them had any detectable clinical improvement occurred. No obvious explanation of this phenomenon comes to mind.

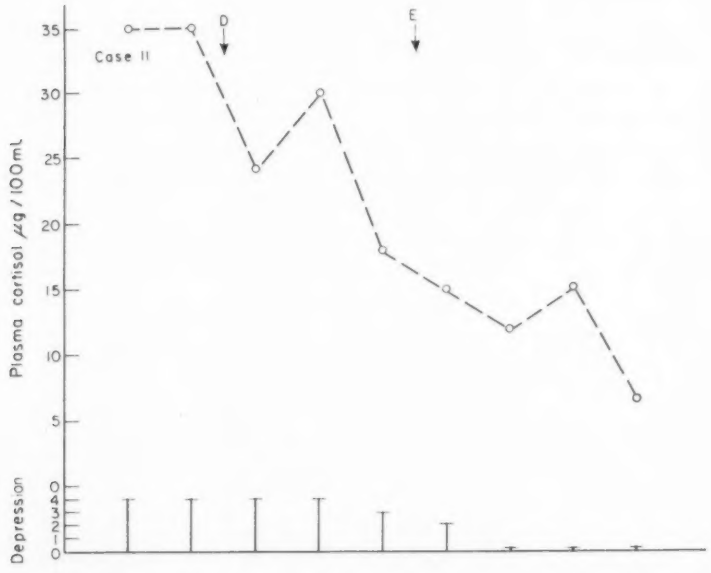

FIG. 2. Weekly plasma cortisol levels and clinical ratings of depression in case 2. Again clinical improvement is accompanied by a gradual decline in plasma cortisol.

In five cases (14 to 18) a definite decline in hormone level did not occur, and they repay closer scrutiny. In three instances (cases 14, 15, 16: see Fig. 3) the levels were consistently rather low. Cases 15 and 16 had only mild depressive symptoms, never being given a high rating and this may account for it. Case 14, however, had symptoms of severe depression and also suffered a sharp relapse, all without any elevation of his plasma cortisol level. It was suggested (on purely clinical grounds and without knowledge of our findings) that he was probably suffering from schizophrenia with depressive features. This can hardly explain our findings, however, since BLISS *et al.*[2] found elevated plasma cortisol levels in schizophrenic patients undergoing emotional turmoil. The same authors pointed out that not every emotional disturbance is associated with increased hormone levels, and they quote the case of one subject, judged to be experiencing extreme tension and anxiety, who had the low plasma level of 6μg/100 ml. It would have been of interest to have measured the plasma ascorbic acid level in our patient if we had been aware at the time of the findings

VOL. 1 1962/

of GROSZ[12], which suggest that an adequate plasma concentration of ascorbic acid is necessary for an optimal adrenocortical response to a stressful stimulus.

In two other patients (cases 17 and 18) hormone levels were consistently rather high. Case 18 was considered to be still rather depressed at the time of his discharge and from his account when he was readmitted it is probable that the severity of his depression was underestimated. In case 17 all depressive symptoms disappeared. The patient, however, had always been an anxious man and he was still anxious at the time of his discharge. It is possible that his persistent anxiety accounted for the absence of a definite decline in plasma cortisol.

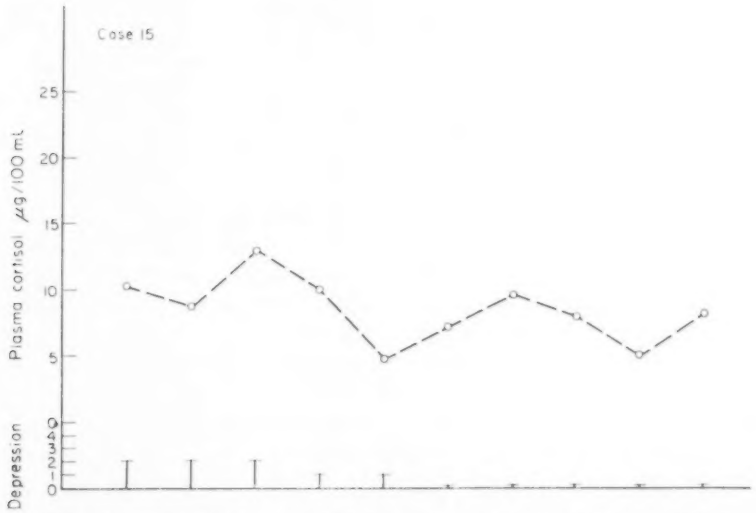

FIG. 3. Weekly plasma cortisol levels and clinical ratings of depression in case 15. Depression was never severe and the plasma cortisol remained essentially unchanged throughout.

None of our patients showed an overall cortisol decline without noticeable improvement. The one patient who remained severely depressed for several weeks (case 11, Fig. 2) had rather variable but persistently high hormone levels during this time. It might be argued that some affective change other than depression — perhaps anxiety or anger — was primarily responsible for the raised levels in our patients. In fact, however, five of the patients with a clinical rating of 4 (cases 1, 2, 5, 8, 12) were retarded depressives without any evidence of anxiety or irritability and a glance at Table 1 shows that their pretreatment levels were no lower than those of the other patients. The mean initial level in this group was 23·7μg/100 ml. The best evidence for a direct relationship between mood and cortisol level is afforded by our cyclothymic patient, case 3. Table 4 shows how each phase of depression was accompanied by high hormone levels, which approached the normal mean when she became well. Her phases of mild elation, in which she was definitely overactive, were accompanied by quite low levels. It may be remarked here that there are scarcely any data in the literature on plasma cortisol levels in untreated manic patients. There is a single report of high values in a patient seen by BLISS *et al.*[2] and we ourselves found a normal

morning level of 12·5μg/100 ml in a hypomanic man. Most manic patients are now very promptly treated with large doses of phenothiazine drugs, which themselves may influence adrenocortical activity.

A possible persistent effect of ECT was looked for by comparing the first hormone level after the beginning of treatment with the immediately preceding one: a significant rise had occurred in four cases, a fall in six, and no change in one. This argues against any consistent effect of ECT and supports the view expressed by BOARD *et al.*[7] ECT does, of course, produce a transient immediate rise in plasma cortisol, the level returning to normal within a few hours[13]. We have not found any evidence in the available literature of a direct effect of imipramine on plasma cortisol. When the five patients who received the drug are considered, it is seen that in two cases (1, 15) there was no obvious change in cortisol levels during the next two weeks. In two other cases (2, 11) there was a sharp fall in plasma cortisol, with a subsequent rise to the previous level after a further one or two weeks: the clinical ratings remained unchanged. In the fifth patient (case 6) falling cortisol levels accompanied clinical improvement. It is possible, then, that imipramine may sometimes induce a transient fall in plasma cortisol without affecting mood. Investigation of a much larger number of patients will be required to clarify this point.

It has been demonstrated that cortisol ordinarily accounts for ninety to ninety-five per cent of the Porter–Silber chromogen measured by the technique used in this investigation[9]. It is just conceivable that some other steroid, or even some other substance might be responsible for the raised levels found in the present investigation. Hence it will be desirable to demonstrate by a more specific method that a rise in true plasma cortisol occurs. Granted that this is so, it has also to be shown that the raised level is due to an increased output of hormone by the adrenal cortex. This has been shown to be the case in the anxious subject (full list of references in PERSKY *et al.*[5]) and preliminary studies with an isotope dilution method derived from that described by Cope and Black suggest that it is true of the depressed patient also.

The limitations involved in the selection of a single point in time in the diurnal cycle of plasma cortisol levels should be borne in mind. Not all individuals have their morning peak level at the same time, and one depressed subject may have a lower 9 a.m. level than another merely because his peak level is attained an hour or two earlier than the other subject's peak. It is also possible that the timing of the peak may alter in an individual subject. A change of this sort would not account for the initial high levels of our patients, but the later declining levels might be a manifestation of an ever earlier morning peak. This seems an unlikely explanation, and it is not supported by our preliminary results with the isotope dilution method already referred to: the increased cortisol output of the depressed patient appears not to be sustained after recovery. The timing of the morning peak and indeed the whole diurnal cycle in depression remains, however, a topic that is worth investigating carefully.

It must be confessed that it is not yet certain that the depressed patient derives any benefit from his raised plasma cortisol concentration. Its biological importance depends in part on whether it is maintained. It has been shown that the raised levels in Cushing's syndrome persist throughout the twenty-four hours[15] whereas in the anxious subjects studied by MASON[8] morning plasma cortisol levels were high but night levels were normal. Even

VOL. 1 1962/

more significant is the extent to which the additional hormone is free or protein-bound, since it is probable that only the free steroid is biologically active[16]. This also is a subject worthy of further investigation.

SUMMARY

Plasma cortisol was measured at weekly intervals in seventeen depressed patients during eighteen periods of stay in hospital.

Elevated levels were found before treatment, and in general the more severe the depression, the higher the cortisol level. In thirteen cases the process of recovery was accompanied by a decline in cortisol levels. The five cases that failed to conform to this pattern are discussed. Details are presented of a cyclothymic patient during three successive cycles of depression and mild elation.

Suggestions are made for further work to assess the degree of adrenocortical activity in depression and to determine its biological importance.

OL.
1
62/63

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VOL.
1
1962/

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THE EXCRETION OF 3-METHOXY-4-HYDROXYMANDELIC ACID IN NORMAL AND IN CHRONIC SCHIZOPHRENIC MALE SUBJECTS

EFFECT OF RESERPINE AND CHLORPROMAZINE

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OL.
1
62/63

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INTRODUCTION

In recent years studies of catecholamines and their metabolites have become a promising area of psychophysiologic research. Such studies have become possible because of clarification of the metabolic fate of free catecholamines *in vivo* and because of the development of suitable methodologies. The major metabolite of epinephrine and norepinephrine, 3-methoxy-4-hydroxymandelic acid (vanillylmandelic acid, VMA), can be accurately measured using a tracer technique developed in this laboratory.[1] The present investigation is primarily a study of the excretion of VMA in normal and in chronic schizophrenic male subjects. The excretion rates of VMA for both groups have been determined under a variety of conditions: ordinary ambulatory activity, bed rest, reserpine administration and chlorpromazine administration. The two drugs employed, reserpine and chlorpromazine, widely used in the treatment of psychoses, have been previously shown to affect catecholamines *in vitro* and *in vivo*.

Creatinine excretion rates have also been determined in order to evaluate the adequacy of urine collections and to ascertain possible renal effects of the drugs employed. The fact that we have observed a difference in creatinine excretion between the normal and schizophrenic subjects necessitates a consideration of creatinine excretion values in this report.

METHODS

Chemical Analyses

Urinary VMA was assayed by the tracer technique described previously,[1] with the exception of the use of a longer column of Dowex 1-acetate (21 in.) and the collection of

a larger forerun of eluate (250 ml) for the fractionation procedure. Urinary creatinine was determined by the alkaline picrate method.[2]

Subjects

The subjects included in these studies numbered seventeen healthy volunteers (Group *N*), ten chronic schizophrenics (Group *S*) and three acute schizophrenics (Group *AS*)—all male.

Table 1.

Group	Age, years		Weight, kg		Duration of Illness (years)	
	Av.	Range	Av.	Range	Av.	Range
N	22·2	19–26	77·2	63·6– 91·4		
S	34·8	27–43	81·1	56·0–123·0	12·8	6 –19
AS	27·0	20–35	72·3	68·2– 78·6	1·2	0·5– 2·9

All in Groups *N* and *S* were hospitalized at the Clinical Center, National Institute of Mental Health, were presented with the same diet, and were under close surveillance by the ward staff. The subjects in Group *AS* were patients at the St. Elizabeths Hospital, Washington, D.C. The *S* subjects had been selected from state hospital patients to participate in biological studies.[3] Of the *AS* subjects, two were diagnosed as catatonic and one as paranoid.

General study procedures

The subjects in Groups *N* and *S* were prohibited from smoking and from ingesting coffee, tea, and "cola" beverages, alcohol and chocolate during and for 24 hr preceding a test procedure. Urine specimens were refrigerated during the collection periods in bottles containing 1 ml of 12 N HCl, their volumes measured at the end of this time, and aliquots frozen until time of analysis. VMA and creatinine determinations were performed on all samples. The results of the analyses have been expressed as ugVMA/kg body weight/hr and as mg creatinine/kg body weight/hr. In those studies in which an intragroup variable was investigated each subject served as his own control and analysis of the data was made on a matched pair basis.

Studies. 1. Three successive 8 hr urine specimens from ten of the *N* group and nine of the *S* group were collected on a day of ordinary ward activities and on a day of bed rest. Diurnal variation within each group was examined under both sets of conditions. The excretion rates of VMA and of creatinine by the two groups during the same time intervals were also compared.

2. The effect of the intramuscular injection of 2·5 mg reserpine was studied in six of the *N* group, five of the *S* group and the three acute schizophrenics. Reserpine was administered at 8 a.m. of the test day and urine specimens were collected during the next 24 hr as follows: 8 a.m. — 12 M., 12 M. — 4 p.m., 4 p.m. — 12 p.m., and 12 p.m. — 8 a.m. Only the 8 a.m. — 12 M. and 12 M. — 4 p.m. specimens were collected for the acute schizophrenics.

VOL. 1 1962/

A placebo (1 ml normal saline, intramuscularly) had been given two days earlier, with all other procedures similar to those employed on the day of reserpine administration.

3. Two hundred mg of chlorpromazine were administered orally to each of ten of the *N* group and ten of the *S* group. Placebo capsules had been administered to these subjects on a previous (control) day. The subjects were confined to bed and three consecutive, 8 hr urine specimens collected on each day.

RESULTS

Intragroup diurnal variation

Mean VMA and creatinine excretion rates for ten *N* and nine *S* subjects during three consecutive 8 hr periods on a day of ordinary ward activities (ambulatory day) and on another day of bed rest are shown in Fig. 1. Statistical analysis of the differences in excretion

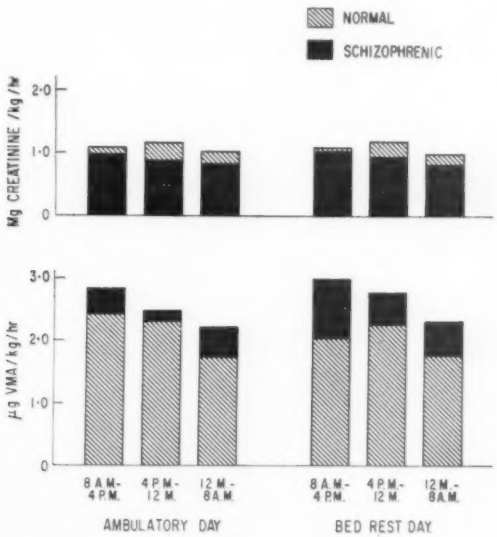

FIG. 1. Mean VMA and creatinine excretion rates for a group of ten normal and nine chronic schizophrenic subjects during consecutive 8 hr periods on a day of ordinary ward activities (Ambulatory Day) and on another day on which the subjects were confined to bed during the day-time periods (Bed Rest Day).

rates between the time periods for each group of subjects under each set of conditions appears in Table 2a. Whether ambulatory or supine during the 8 a.m. — 4 p.m. and 4 p.m. — 12 p.m. periods, each group excreted less VMA during the 12 p.m. — 8 a.m. period than the other two periods, although the difference in the VMA excretion rates between the 4 p.m. — 12 p.m. ambulatory period and the 12 p.m. — 8 a.m. period of the *S* group was not significant.

Significant diurnal changes in creatinine excretion rates occurred only under conditions of bed rest: each group excreted creatinine at a greater rate during the day-time periods

TABLE 2. STATISTICAL ANALYSIS OF MEAN VMA AND CREATININE EXCRETION VALUES FOR TEN NORMAL (*N*) AND NINE CHRONIC SCHIZOPHRENIC (*S*) SUBJECTS

a. Diurnal Variation: Subjects Studied on a Day of Normal Ward Activity (Amb.) and on a Day of Bed Rest (B.R.)

Periods Compared	Determination	μg VMA/kg/hr Amb. *N*	Amb. *S*	B.R. *N*	B.R. *S*	mg Creatinine/kg/hr Amb. *N*	Amb. *S*	B.R. *N*	B.R. *S*
8 a.m.–4 p.m. (1) & 4 p.m.–12 p.m. (2)	△	0·13	0·35	−0·20	0·23	−0·05	0·10	−0·12	0·09
(1)–(2)	*SED*	0·091	0·252	0·135	0·164	0·416	0·108	0·063	0·036
	t	1·428	1·389	−1·481	1·402	−1·202	0·926	−1·905	2·500*
8 a.m.–4 p.m. (1) & 12 p.m.–8 a.m. (3)	△	0·68	0·62	0·28	0·69	0·08	0·16	0·10	0·22
(1)–(3)	*SED*	0·126	0·218	0·074	0·176	0·126	0·079	0·027	0·036
	t	5·397***	2·844*	3·784***	3·920***	0·635	2·089	3·704***	6·111***
4 p.m.–12 p.m. (2) & 12 p.m.–8 a.m. (3)	△	0·55	0·27	0·48	0·46	0·13	0·07	0·22	0·12
(2)–(3)	*SED*	0·151	0·236	0·107	0·173	0·065	0·055	0·046	0·044
	t	3·642***	1·144	4·486***	2·659*	2·000	1·273	4·738***	2·727*

b. Comparison of Excretions by Normal and Schizophrenic Subjects

Period	Determination	μg VMA/kg/hr Amb.	B.R.	mg Creatinine/kg/hr Amb.	B.R.
8 a.m.–4 p.m.	△(*S*–*N*)	0·40	0·96	−0·10	−0·04
	SED	0·301	0·327	0·065	0·065
	t	1·329	2·936***	−1·538	−0·615
4 p.m.–12 p.m.	△(*S*–*N*)	0·18	0·53	−0·25	−0·25
	SED	0·344	0·318	−0·091	0·070
	t	0·523	1·667	−2·747***	−3·571***
12 p.m.–8 a.m.	△(*S*–*N*)	0·47	0·55	−0·19	−0·16
	SED	0·250	0·255	0·065	0·061
	t	1·880	2·157*	−2·923***	−2·623**

Key to Abbreviations and Symbols: *SED*, standard error of the difference; *t*, value obtained using Fisher's test for significance of difference; *** $P<0·01$; ** $P<0·02$; * $P<0·05$.

VOL. 1 1962

than during the night period; in addition, the *S* group showed a greater excretion rate during the 8 a.m. — 4 p.m. period than during the 4 p.m. — 12 p.m. period.

Effect of Bed Rest on Excretion Rates of Each Group (*Fig.* 1). The VMA excretion rate for the *N* group was significantly lower during the 8 a.m. — 4 p.m. period of bed rest than during the same period of ambulatory activity ($P<0{\cdot}01$). The *S* group evidenced no significant effect of bed rest on VMA excretion rates during any period. The creatinine excretion rates of each group were unaffected by the test conditions.

Comparison of excretion rates by the N *group with those of the* S *group* (*Fig.* 1, *Table* 1*B*)

Although the mean VMA excretion rate of the *S* group exceeded the mean rate of the *N* group for each period studied, the difference between the excretion rates of these two groups was significant only during the 8 a.m. — 4 p.m. and the 12 p.m. — 8 a.m. periods on the day of bed rest.

Significant differences in creatinine excretion rates between the *N* and the *S* subjects occurred during the 4 p.m. — 12 p.m. and the 12 p.m. — 8 a.m. periods on both test days. This difference was further evaluated by expressing the creatinine excretion rates in relation to non-fat weight. The following equation, derived from data obtained by BROZEK and KEYS,[4] was used for calculating relative non-fat weight:

$$RNFW = 0{\cdot}975\ RW - 0{\cdot}005\ (\text{Age} - 21)$$

where, $RNFW$ = relative non-fat weight
and, RW = relative weight = 100 × actual weight/standard weight for sex, age and height. When creatinine excretion was expressed per unit of non-fat relative weight, the excretion rates for the 24 hr period were identical for both groups: 0·775 mg creatinine/unit of non-fat relative weight/hr. Thus it appears that the observed differences in creatinine excretion per unit of total weight are explicable on the basis of body constitution and do not implicate any difference in creatinine metabolism.

Effect of reserpine administration

The effect of the intra-muscular injection of 2·5 mg of reserpine on VMA and creatinine excretion rates was studied in six of the *N* subjects, five of the *S* subjects and the three *AS* subjects. The data obtained for the first two groups appear in Table 3. A highly significant increase in VMA excretion rate occurred during the first two 4 hr periods following administration of the drug in both groups; there was no significant difference in the VMA response to this dose of reserpine between the two groups. Following reserpine administration, creatinine excretion rates were depressed in the *N* subjects during the 12 M.—4 p.m. and the 4 p.m.—12 p.m. periods. A significant difference between the *N* and *S* subjects in effect of reserpine on creatinine excretion during the 12 M.—4 p.m. period emerged. The decrease in creatinine excretion in the *N* group, unassociated with a subsequent increase, suggests a decrease in the creatinine clearance rather than incomplete urine collections. In spite of this implied decrease in glomerular filtration rate, there was a marked increase in the rate of VMA excretion.

The effect of the same dosage of reserpine on VMA and creatinine excretion rates by

TABLE 3. EFFECT OF RESERPINE ADMINISTRATION ON MEAN VMA AND CREATININE EXCRETION VALUES FOR SIX NORMAL (*N*) AND FIVE CHRONIC SCHIZOPHRENIC (*S*) SUBJECTS

Period	Determination	μg VMA/kg/hr					mg Creatinine/kg/hr				
		N	*S*	*S–N*	*SED*	*t*	*N*	*S*	*S–N*	*SED*	*t*
8 a.m.–12 M.	Placebo (P)	2·30	2·78				1·10	1·16			
	Reserpine (R)	3·42	3·93				1·03	1·11			
	△(R–P)	1·12	1·15	0·03	0·127	0·236	−0·07	−0·05	0·02	0·135	0·148
	SED	0·177	0·145				0·107	0·071			
	t	6·328***	7·931***				−0·654	−0·704			
12 M.–4 p.m.	Placebo (P)	2·30	2·33				1·12	0·88			
	Reserpine (R)	3·89	3·56				0·98	0·88			
	△(R–P)	1·59	1·23	−0·36	0·244	−1·475	−0·14	0·00	0·14	0·029	4·828***
	SED	0·167	0·176				0·024	0·015			
	t	9·521***	6·989***				−5·833***	0·00			
4 p.m.–12 p.m.	Placebo (P)	2·69	2·31				1·14	0·96			
	Reserpine (R)	2·70	2·29				0·97	0·79			
	△(R–P)	0·01	−0·02	−0·03	0·337	−0·089	−0·17	−0·17	0·00		0·00
	SED	0·220	0·247				0·064	0·081			
	t	0·0455	−0·081				−2·656*	−2·099			
12 p.m.–8 a.m.	Placebo (P)	2·33	1·94				0·99	0·87			
	Reserpine (R)	2·14	2·21				1·00	0·93			
	△(R–P)	−0·19	0·27	0·46	0·310	1·484	0·01	0·06	0·05	0·065	0·769
	SED	0·205	0·222				0·036	0·060			
	t	−0·927	1·216				0·278	1·000			

VOL. 1 1962

the three *AS* subjects is shown in Table 4. The small size of this population prohibits useful statistical evaluation of the data; examination of the VMA response to reserpine, however, suggests no difference between the *AS* group and the other two groups. The decreased

TABLE 4. EFFECT OF RESERPINE ADMINISTRATION ON MEAN VMA AND CREATININE EXCRETION VALUES FOR THREE ACUTE SCHIZOPHRENIC SUBJECTS

		μg VMA/kg/hr	mg Creatinine/kg/hr
8 a.m.–12 M.	Placebo (P)	1·92	1·25
	Reserpine (R)	2·54	1·21
	△(R–P)	0·62	−0·04
12 M.–4 p.m.	Placebo (P)	1·52	1·31
	Reserpine (R)	2·61	1·13
	△(R–P)	1·09	−0·18

OL.
1
62/63

excretion of creatinine during the 12 M.—4 p.m. period following reserpine administration was similar to that exhibited by the *N* subjects.

Effect of chlorpromazine administration

The effect of the ingestion of 200 mg chlorpromazine on mean VMA and creatinine excretion rates by ten *N* and ten *S* subjects is shown in Table 5. On the day of drug administration, the *N* subjects maintained a decreased rate of VMA excretion throughout the three 8 hr periods studies; unaltered creatinine excretion rates indicate that renal or urine collection factors were not responsible for the decreased VMA excretion rate by this group.

The *S* subjects showed a decreased VMA excretion rate during the first two 8 hr periods following chlorpromazine ingestion. However, the decrease in creatinine excretion rate indicated that, in this case, renal excretory function rather than catecholamine metabolism could be responsible. During the 4 p.m.—12 p.m. period, the decrease in VMA excretion rate was not accompanied by a decrease in creatinine excretion rate indicating a true effect of the drug on catecholamine metabolism. The effect of chlorpromazine administration on VMA excretion rates was the same for the *N* group as for the *S* Group for each 8 hr period as well as for the composite 24 hr period.

DISCUSSION

Epinephrine and norepinephrine are altered so rapidly *in vivo* that only a few per cent of an administered dose can be accounted for in subsequent urine specimens.[5,6] The application of tracer techniques has provided much information about metabolic pathways involved in the degradation of an infused radioactive catecholamine. Following infusion of radioactive epinephrine or norepinephrine, twenty-three to fifty-nine per cent of the isotope appearing in the urine is present in the VMA fraction.[7,8] Indications are that a

TABLE 5. EFFECT OF CHLORPROMAZINE ADMINISTRATION ON MEAN VMA AND CREATININE EXCRETION VALUES FOR TEN NORMAL (*N*) AND TEN CHRONIC SCHIZOPHRENIC (*S*) SUBJECTS

Period	Determination	μg VMA/kg/hr					mg Creatinine/kg/hr				
		N	*S*	*S–N*	*SED*	*t*	*N*	*S*	*S–N*	*SED*	*t*
8 a.m.–4 p.m. (1)	Placebo (P)	2·02	2·81				1·11	0·99			
	Chlorpromazine (CPZ)	1·68	2·39				1·06	0·86			
	△(CPZ–P)	−0·34	−0·42	−0·08	0·211	−0·379	−0·05	−0·13	−0·08	0·066	−1·212
	SED	0·133	0·163				0·038	0·054			
	t	−2·556*	−2·577*				−1·316	−2·408*			
4 p.m.–12 p.m. (2)	Placebo (P)	2·10	2·77				1·17	0·94			
	Chlorpromazine (CPZ)	1·79	2·25				1·11	0·96			
	△(CPZ–P)	−0·31	−0·52	−0·21	0·170	−1·235	−0·06	0·02	0·08	0·075	1·067
	SED	0·119	0·122				0·043	0·061			
	t	−2·605*	−4·262***				−1·395	0·328			
12 p.m.–8 a.m. (3)	Placebo (P)	1·66	2·32				0·97	0·82			
	Chlorpromazine (CPZ)	1·51	2·40				0·97	0·90			
	△(CPZ–P)	−0·15	0·08	0·23	0·169	1·361	0·00	0·08	0·08	0·050	1·600
	SED	0·053	0·155				0·028	0·047			
	t	−2·830**	0·516				0·00	1·702			
8 a.m.–8 a.m.	Placebo (P)	1·93	2·63				1·08	0·92			
(1), (2) and (3)	Chlorpromazine (CPZ)	1·66	2·34				1·05	0·91			
	△(CPZ–P)	−0·27	−0·29	−0·02	0·106	−0·188	−0·03	−0·01	0·02	0·025	0·800
	SED	0·055	0·091				0·021	0·014			
	t	−4·909***	−3·187**				−1·428	−0·714			

VOL. 1 1962

much larger percentage of endogenously released catecholamine is converted to VMA, since more than seventy times as much VMA is found in the urine[1,9] as is epinephrine plus norepinephrine.[10,11] For this reason, we have undertaken these studies of VMA excretion and have interpreted the results to be indicative of overall catecholamine release.

In this report, VMA excretion has been expressed as μg VMA/kg of body weight/hr. Introduction of the weight factor seemed desirable as an approximate correction factor for total metabolizing tissue. Some investigators, including ourselves, have expressed VMA excretion in relation to creatinine excretion on the assumption that urine collection and/or renal excretory factors are potential determinants. Earlier observations made in this laboratory on a group of normal male subjects indicated that the individual's creatinine excretion rates were remarkably consistent (coefficient of variation for 24 hr values = $\pm$3·5 per cent) and were therefore useful in revealing alterations in renal function and/or incomplete voiding.[12] A high degree of consistency in creatinine excretion rates observed under comparable test conditions is not surprising, since endogenous creatinine clearance in man closely approximates the glomerular filtration rate as determined by inulin clearance.[13–16] In the present study, the VMA/creatinine ratio has not been tabulated because of the difference in creatinine excretion between the two groups of subjects. The creatinine excretion rates for each individual have been assessed and the values presented have been judged to be based on complete urine collections. MCDONALD,[17] reporting initial results on VMA excretion in schizophrenic and non-schizophrenic subjects found a significant difference between the two groups with respect to μg VMA/mg creatinine and mg creatinine/kg/24 hr, but not in μg VMA/kg/24 hr, thereby implying that the difference between the groups was not related to VMA excretion and that expression of the results as the creatinine ratio was misleading.

The difference in creatinine excretion rates between the schizophrenic and normal subjects, previously reported[17] and herein confirmed, appears to be explicable on the basis of differences in body composition. Using the data of BROZEK and KEYS,[4] the heavier and older schizophrenic subjects have been calculated to have 15·8 per cent more fat than the normal subjects; their creatinine excretion rates/kg of body weight are 16·7 per cent less than those of the normal subjects. Expression of creatinine excretion rates in terms of non-fat body weight reveals that there is no difference between the *S* subjects and the *N* subjects in this function and strongly implies that the significant factor is the degree of fatness.

The diurnal variation in VMA excretion by normal subjects reported elsewhere [1,18,19] is again observed. The schizophrenic subjects studied here exhibited a diurnal trend in VMA excretion which was similar to, though less consistent than, that of the normal subjects.

The mean VMA excretion rates of the *S* subjects exceeded those of the *N* subjects for each time period studied. On the day of ordinary ambulatory activities, the 24 hr VMA excretion rate was 16·6 per cent higher for the *S* group than for the *N* group. This difference is not significant. However, during the day of bed rest, the VMA excretion of the *S* subjects rate was 34·2 per cent ($P < 0{\cdot}05$).

KÄRKI [20] reported that muscular activity results in remarkably increased excretions of epinephrine and norepinephrine. The present finding of a greater rate of VMA excretion by the normal subjects when participating in the comparatively mild physical exertion attending ordinary ward activities than when in bed is compatible with the report of

Kärki[20] although the latter study was concerned with a far more vigorous type of activity. The schizophrenic subjects, on the contrary, excreted VMA at a greater rate when they were confined to bed than when free to pursue their usual activities.

The injection of a single dose of reserpine resulted in an increased release and/or synthesis of catecholamine, as is evidenced by a greatly enhanced excretion of VMA for approximately 8 hr following administration of the drug. No difference in rates of VMA excretion was noted between the normal and schizophrenic subjects. Gaddum *et al.*[21] and Carlsson *et al.*[22] have found that male schizophrenic patients being chronically treated with reserpine have decreased urinary norepinephrine levels with either decreased or unchanged epinephrine excretions. Muscholl and Vogt[23] and De Schaepdryver[24] have shown that a single dose of reserpine administered to animals causes tissue depletion of catecholamines and a temporary increase in blood and urinary catecholamines, findings which are compatible with those of this study. McDonald and Weise (unpublished observations), in attempting to clarify the apparent difference between the effect of a single dose of reserpine and that of repeated doses, have found that serial injections in man are associated with an initial increase in VMA excretion followed by a decrease.

Chlorpromazine administration decreases VMA excretion rate to the same extent in both normal and schizophrenic subjects. Although the mechanisms of chlorpromazine action on VMA excretion have not been demonstrated, certain relevant studies should be considered. Axelrod *et al.*[25] have shown that chlorpromazine administration to cats inhibits the uptake of administered H^3-norepinephrine by certain tissues while causing an increased concentration in the plasma. However, when chlorpromazine is administered following an infusion of H^3-norepinephrine in rats, it has no effect on the tissue content of the radioactive catecholamine.[26] Gey and Pletscher[27] have demonstrated that the endogenous norepinephrine content of rat brain is not affected by the administration of chlorpromazine, and that enzymes involved in the synthesis (decarboxylase) and degradation (monoamine oxidase) are not inhibited *in vivo* by the drug. O-Methyl transferase, the other enzyme required for the production of VMA from catecholamine is unaffected by chlorpromazine administration.[28] In view of these reports it is possible that the decreased VMA excretion observed in the present studies results from a decreased accessibility of the circulating catecholamines to tissue sites where metabolism occurs. Under these circumstances one would expect to see increased excretion of free catecholamines associated with the decreased VMA excretion.

SUMMARY

The following observations have been made on the excretion of 3-methoxy-4-hydroxymandelic acid (VMA) in normal and chronic schizophrenic male subjects:

1. Significant diurnal changes in VMA excretion rate occurred in both normal and chronic schizophrenic subjects. The VMA excretion rate was greater during the waking hours (8 a.m.—12 p.m.) than during the sleeping hours (12 p.m.—8 a.m.); this difference was not a function of the physical activity attending ordinary ambulatory activity.
2. The chronic schizophrenic subjects tended to have a higher VMA excretion rate

VOL. 1 1962/

than the normal subjects, and the difference in excretion rates was significant when the subjects were kept on a 24 hr period of bed rest.

3. The chronic schizophrenic subjects excreted less creatinine than the normal subjects. It is suggested that this difference is due to a difference in body composition between the two groups.

4. Reserpine administration causes a similar increase in VMA excretion in both groups of subjects.

5. Chlorpromazine administration causes a similar decrease in VMA excretion in both groups of subjects.

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VOL.
1
1962/

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EFFECTS OF PERCEPTUAL ISOLATION ON INTROVERTS AND EXTRAVERTS

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OL.
1
62/63

RECENTLY there has been increasing attention directed to "perceptual isolation" or "sensory deprivation" as a stressful condition. Extensive reviews of this literature are available in other sources (SOLOMON, *et al.*[1]) and will not be repeated here.

Within the framework of Jungian theory, sensory deprivation phenomena such as hallucinations and daydreams can be interpreted as concomitant features of the process of introversion. When the environment becomes very stressful by virtue of its ambiguity, there is a turning away from reality to fantasy. If there is no meaningful information in the environment there is no way for the ego to mediate between unconscious forces and external reality. Action and judgment are no longer possibilities, consequently there must be some substitute for action. This substitute is provided by the introverted type of thinking with the ascendance of the "archaic forces of the unconscious" in the form of hallucination, fantasy, changes in affect, daydreams.

Out of this formulation arises a question regarding the reactions of the individual whose usual attitude is introversive, in the Jungian sense, to the conditions of perceptual isolation. If introversion refers to a progressive withdrawal from reality, it should be expected that individuals on the extreme end of this dimension would be little affected by sensory alterations and perceptual changes in the environment. It is the purpose of this study to investigate the following hypotheses:

1. Introverts are able to tolerate perceptual isolation better than extraverts.
2. Introverts show smaller changes in emotional experiences as a function of perceptual isolation than do extraverts. For the purposes of this study, a change in emotional experience is defined as a change in ratings of words on the Semantic Differential.

METHOD

Subjects

Subjects used in the study were selected on the basis of their scores on the Myers-Briggs Type Indicator.[2] This is a group administrable paper-pencil personality test designed within the framework of Jungian theory. It was administered to a group of 318 male

* Data of this study were used as part of the author's Ph.D. thesis. The project was supported in part by a research grant from Washington State University.

undergraduate students at the University of South Dakota. Their scores on the introversion-extraversion scale ranged from −27 to +27. The mean was −0·303 and the standard deviation was 12·5. For the purposes of this study, introverts and extraverts were defined as those subjects who had scored 1·5 standard deviations or more beyond the mean on the Myers-Briggs Type Indicator. A total of 40 *S*s, 20 introverts and 20 extraverts, were available for the entire experimental procedure. In order to provide two scores on the Semantic Differential, 10 *S*s of each group were randomly assigned to a control group. The *S*s ranged in age from 18 to 29 with a mean age of 20.

Apparatus

The semantic differential. The semantic differential used for the study followed the form developed by OSGOOD, *et al.*[3] The form used in this study was composed of 16 concepts and each was to be assigned a rating on 16 scales. The concepts included two groups of words: One group consisting of eight emotionally descriptive abstract nouns, the other of eight abstract nouns not emotionally descriptive. The two lists were equated for familiarity by checking them against the Thorndike-Lorge Frequency Count.[4] The list of emotional words consisted of boredom, fear, worry, anger, grief, loneliness, anxiety, frustration. The nonemotional words were sample, survey, system, situation, formation, structure, metal, frequency.

Description of the room. The room used for the 20 experimental *S*s was an 8 × 7 × 9 ft sound-treated room used for conducting hearing tests. Illumination was provided by a 60-watt bulb placed 5 ft from *S*s eyes. This light was diffused by a piece of heavy asbestos 12 × 24 in. in size suspended 3 in. from the light.

White noise was administered through a set of headphones by a Grason-Stadler, 950-C Twin Oscillator. This noise was compared with a 70 dB complex noise generated by Maico H-1 audiometer in order to obtain the level of loudness at which the white noise was to be presented. The white noise and the sound-treated room excluded all ambient noise from the subjects.

Halved pingpong balls were affixed to *S*s eyes. A pair of perforated rubber gloves was placed on his hands and his arms were placed in cardboard cuffs extending from the elbow to beyond the finger-tips. A recording was made for each *S* of all vocal sounds and audible movements produced while he was in the room. This was accomplished through a microphone placed in the room and connected to a tape recorder through a noise relay. In this way a comparable, quantifiable record of audible events was obtained for each *S*.

Procedure

All 40 *S*s reported two weeks before the experiment for the first administration of the Semantic Differential and for scheduling an appointment for the experiment. When each experimental subject reported for his appointment he was taken to the experimental room and given the following instructions:

"Lie here as motionless as you can. Keep your eyes open and don't go to sleep. Every time you think a half hour has passed, say "half an hour is up." The microphone which you may have noticed here on the wall is connected to a tape recorder oustide the room and your half-hour estimates will be recorded. Feel free to express any other thoughts or

VOL.
1
1962/

feelings whenever you like. The experiment will last all afternoon, but you can terminate it anytime you feel you really must."

S was observed at all times while in the room. He was awakened by a sudden, brief increase in the intensity of the white noise if: (1) he overestimated a half-hour period by more than 20 min and there was no movement in the room, or (2) he was obviously sleeping as judged by his constant, heavy breathing.

The subject remained in the room for 4 hr or until he voluntarily terminated the experiment, whichever occurred first. After leaving the room he was immediately given the second administration of the semantic differential. He was then interviewed by the experimenter using a standard form for all *S*s.

When control subjects reported for their appointments they were not placed in the isolation room but were again given the semantic differential and after completing this, they were given the MMPI. The control group was needed only to provide a basis of comparison of scores on the Semantic Differential. This group was not put in the isolation room. The comparison on all sources of data except the Semantic Differential was made by comparing extraverts and introverts who were in the isolation room. All subjects were paid at the rate of $1.15 per hour for all time spent in the experiment.

Data were provided by the following five sources:

a. Length of time spent in the isolation room.
b. The post-isolation interview.
c. Observations and recordings of audible events during *S*'s stay in isolation.
d. Change scores on the semantic differential.
e. The Minnesota Multiphasic Personality Inventory. The MMPI was administered to provide a clinical description of the two groups of subjects.

RESULTS

1. Time in the room. As a group, extraverts tolerated the isolation conditions significantly better than introverts in terms of time spent in the room. Eight of the extraverts, but only one of the introverts remained the entire 4 hr. Comparison of the "stay" and "quit" groups is shown in Table 1.

Table 1. NUMBER OF SUBJECTS REMAINING THROUGH OR QUITTING THE 4 HR STAY IN ISOLATION

Group	Extraverts	Introverts
Stay	8	1
Quit	2	9

Applying Fisher's exact probability test,[5] the probability of this outcome and of all more deviant outcomes in either direction is 0·014. This finding did not support Hypothesis One — introverts are able to tolerate perceptual isolation better than are extraverts.

2. The Post-isolation interview. Data obtained from the interview were analyzed most appropriately in a qualitative way. These data consisted of the following statements made by the two groups.

Extraverts

R.B.: "I thought I was in there for experimental purposes; I could have stayed longer but I have exams coming up; it didn't bother me too much".

T.D.: "I guess I could have stayed all night. Seemed like I was only in there about 2 hr. I don't think I slept but I was relaxed".

L.L.: "At first it felt calm, like when I went up in a decompression chamber in the Air Force. I felt like sleeping. The pay made no difference, I wouldn't do it just for the money".

M.M.: "I thought it was kind of a challenge. I figured you wanted to see how long I could stay".

R.M.: "It was very relaxing, almost too relaxing. I was able to relax and forget my troubles".

L.S.: "It reminded me of something in the movies like a Korean Prisoner of War or something. I've been through rough things before so I didn't leave".

C.T.: "Seemed like a test of endurance, seemed like a test of resistance against boredom. Wanted to see how close I could estimate the time".

P.H.: "I knew I gave too many estimates but thought I could maybe make the time go by if I threw in a few extra half-hours."
At 1 hr: complained about need for cigarette; at 2 hr 10 min: raised arms and waved them about in a fanning motion; at 2 hr 25 min: buried head in pillow; at 2 hr 30 min: felt glasses, "These damn things"; at 2 hr 55 min: tried to reach for the light; at 3 hr 15 min: moved the microphone up and down in its stand.

J.G.: "Thought I was in a space ship once. It felt like I was movin' real fast, like maybe in a rocket ship".

F.S.: "This is the biggest waste of time I've ever seen".

Introverts

S.B.: "I found it difficult to breathe towards the end. Thought I was in there to see how the noise would affect a person".

G.D.: "I didn't know what was on my hands. I didn't know what to do, whether you wanted me to talk or not".
(After 1 hr 45 min: "I think I've made my contribution for to-night".)

T.I.: "I was most uncomfortable, my hands felt boxed up. I didn't think I'd last the full half hour".

D.L.: "Didn't like laying still; kept getting more restless. I thought maybe you were cutting people off from the world to see what happens to them".

C.L.: "I thought the whole situation was kinda ridiculous".

B.S.: "I was nervous due to all the equipment and I wondered what kind of approach I'd use".

K.S.: "I was a little shaky at the end and had a slight headache. I thought maybe you expected me to panic; maybe you wanted to see how stable a person is".

S.W.: "You asked me not to move so I didn't. I could have stayed longer if I could have moved".

VOL.
1
1962/

T.L.: "I thought about getting mad but knew I couldn't get too mad because I could leave anytime".

T.V.: "I laid for a long time not thinking about anything; I couldn't think of anything".

These data, in general, suggest that the extraverts tended to regard the situation as a challenge, while introverts regarded it as a stressful condition. Most *S*s reported difficulty in concentrating or in maintaining consistent thought patterns. *S*s in both groups reported pleasant as well as unpleasant thoughts.

Their comments also indicate that those *S*s who remained in the room longest were able to engage in some form of pleasant reverie. None of the introverts mentioned remote past experiences as part of their thought patterns. This group concentrated on what might be called "stimulus bound" thought. Attention was devoted to the room, the equipment, the purpose of the experiment. Extraverts, on the other hand, mentioned experiences more removed from the present situation, e.g., "my girl", "my buddies", "getting drunk", "high-school days". There was no mention of hallucinations or dreams made by any member of either group.

3. Observations and recordings of audible events. In general, the extraverts reacted by ignoring the instructions to "lie quietly and estimate the time each half hour", while the introverts reacted by attempting to adhere rigidly to instruction. This result is indicated by the fact that 10 of the extraverts who spoke during isolation mentioned difficulty in staying awake. None of the introverts mentioned such a difficulty.

In addition, extraverts made more movements per minute than did the introverts. While this difference was not statistically significant, the tendency of the extraverts to sleep would decrease the number of movements for this group even if sleep did not actually occur. Comparison of the number of movements per minute made by the two groups is shown in Table 2.

TABLE 2. COMPARISON OF NUMBER OF MOVEMENTS MADE BY EXTRAVERTS AND INTROVERTS

Group	Mean movements per minute	Mean difference	Standard error of mean difference	t[a]
Extravert	0·3834			
Introvert	0·2315	0·152	0·11	1·39

[a] For 18 degrees of freedom, t = 1·73 is significant at the 0·05 level of confidence for a one-tail test.

Introverts also spoke of a greater degree of discomfort during isolation than did extraverts. Eight members of this group complained about discomfort caused by lack of movement and 4 of them spoke about quitting before putting their desires into action. None of the extraverts spoke of quitting, and this latter group also moved about sufficiently to alleviate discomfort caused by lying in one position even though this was in violation of instructions.

This finding, of difficulty in staying awake and violation of instructions among the extraverts, and greater discomfort and tendency to quit among the introverts, did not support Hypothesis One.

4. The Semantic Differential. Data on the semantic differential were analyzed by

calculating "factor change scores" for each subject. That is, changes in ratings from pre- to post-testing were obtained by algebraically summing change scores on each of four factors for emotional and non-emotional words separately. The four factors included were those previously identified by OSGOOD *et al.*[3] as activity, potency, evaluative, and stability.

As shown in Table 3, an analysis of variance of these data indicated that there was no

TABLE 3. ANALYSIS OF VARIANCE OF FACTOR CHANGE SCORES FROM PRE- TO POST-ISOLATION TESTING ON THE SEMANTIC DIFFERENTIAL

Source of Variation	Sum of Squares	df	Mean Square	F[a]
Experimental-Control	708·06	1	708·06	2·079
Extraversion-Introversion	1193·52	1	1193·52	3·504
Experimental-Control by Extraversion-Introversion	288·80	1	288·80	<1
Subjects within Groups	12260·34	36	340·57	
Emotional-Nonemotional	12·80	1	12·80	<1
Between Factors	1085·11	3	361·70	2·71
Emotional-Nonemotional by Factors	730·64	3	243·55	1·900
Subjects by Emotional-Nonemotional	10378·07	39	266·10	2·076
Subjects by Factors	15625·76	117	133·55	1·042
Residual	14997·49	117	128·18	
Total		319		

[a] For 1 and 36 degrees of freedom, F = 4·11 is significant at the 0·05 level of confidence. For 3 and 117 degrees of freedom, F = 2·69 is significant at the 0·05 level of confidence. For 39 and 117 degrees of freedom, F = 1·87 is significant at the 0·01 level of confidence.

significant between-groups difference in ratings of words on the semantic differential. This result was interpreted to mean that the words were not rated differently by the two groups from the pre- to post-isolation testing. This result did not confirm Hypothesis Two: Introverts show smaller changes in emotional experiences as a function of perceptual isolation than do extraverts.

5. The MMPI. The MMPI resulted in a code of 96–345 78 1/20: for the extraverts. In general, the shape of this profile indicated that members of this group presented themselves in a somewhat guarded fashion as very active, trouble-free, poised, socially adept, optimistic individuals who are unusually suspicious and mildly disdainful of customary social standards. The most striking feature of their profile was that scale 5 (Paranoia) was relatively and absolutely a high point in the code. This, plus a very low score on scale 0 (Social Introversion) suggested an unusual degree of interpersonal sensitivity among these subjects.

For the introverts the mean MMPI profile was 507–28 46 19/3. The shape of this profile indicated that this group presented themselves candidly as experiencing an unusual degree of discomfort in social situations. They have a more feminine interest pattern and are

VOL.
1
1962/

more passive and dependent than the extraverts. They are prone to ruminate and reflect on their own problems and generally experience an unusual amount of anxiety and discomfort.

DISCUSSION

The results of the study indicated that there were striking contrasts between the two groups in their reactions to the experimental condition. In general, the introverts reacted to the condition by leaving it, whereas the extraverts reacted by restructuring it. The introverts perceived the experimental condition as uncomfortable, but they followed the instructions to "lie quietly and don't go to sleep" more closely than did the extraverts. The introverts were more preoccupied with "stimulus bound" thought, that is, they attended more closely to the immediate experimental situation. As a result they reported greater discomfort while in the room than did the extraverts. They did not become as sleepy, and at the same time, they did not move about as much while awake. In other words, the introverts responded to the situation by accepting the specified condition but they left it after it became too difficult to tolerate.

The extraverts perceived the experimental condition as a challenge and in general they remained in it for the specified period of time. In contrast to the introverts they responded to the situation by rejecting the specified conditions. They tended to go to sleep, to move about while awake, to engage in some form of pleasant reverie, and to whistle or hum tunes. As a result, they reported less discomfort while in the room than did the introverts.

Since the introverts left the situation and the extraverts modified it by disobeying instructions, it is difficult to draw definitive conclusions about the actual effects of perceptual isolation on these groups. The evidence does suggest, however, that personality factors measured by the Myers-Briggs Type Indicator are predictive of response to conditions of perceptual isolation. This is a finding which remains to be validated by future work.

The results of this study also emphasize the severe methodological problems involved in research on perceptual isolation. Investigators have tended to use time spent in isolation as a criterion of tolerance. The present data suggest that this criterion may not be the most appropriate measure of tolerance. If some subjects are able to remain in isolation for a long period of time they may do so partly because they do not actually experience isolation conditions. Response measures indicating what the subject does while in isolation may be more appropriate to index tolerance limits.

The results also indicated that the Semantic Differential was not appropriate as a measure of the kinds of changes that occurred under these conditions.

SUMMARY

This study utilized 40 *S*s, 20 extraverts and 20 introverts, in an investigation of the reactions of extraverts and introverts to perceptual isolation. Ten subjects of each group were subjected to perceptual isolation by being placed in a sound-treated room with white noise fed into their ears, halved ping-pong balls affixed to their eyes, and rubber gloves and cardboard cuffs on their hands. They remained in the room for 4 hr or until they voluntarily terminated the experiment, whichever occurred first.

Reactions of the two groups to perceptual isolation were measured by (1) changes in ratings of words on the semantic differential, (2) length of time spent in the isolation room, (3) tape recordings of audible events during *S*'s stay in isolation, and (4) a post-isolation interview. The following two hypotheses were tested:

1. Introverts are able to tolerate perceptual isolation better than are extraverts.
2. Introverts show smaller changes in emotional experiences as a function of perceptual isolation than do extraverts.

The findings of this study were as follows:

1. In general, introverts and extraverts showed markedly different reactions to perceptual isolation.
2. Reactions of introverts were characterized by leaving the isolation room, but while in the room, this group adhered closely to instructions, tended to engage in "stimulus-bound" thought, remained awake and did not move about.
3. Reactions of extraverts were characterized by remaining in the room for the specified period of time, but while in the room, this group tended to violate instructions, to engage in some form of pleasant reverie, to go to sleep, and to move about while awake.
4. As measured by the semantic differential, changes in emotional experiences as a function of perceptual isolation were not significantly different for the two groups.
5. Characteristic phenomena — hallucinations, delusions, fantasy — usually reported in isolation studies, failed to occur.

It was concluded that criteria of tolerance for perceptual isolation are generally so ambiguous that Hypothesis One was not clearly confirmed. Hypothesis Two was not confirmed by results of the semantic differential. The two groups of subjects showed markedly different reactions to the experimental condition and these reactions were not inconsistent with Jungian theory, on which the hypotheses were based.

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VOL.
1
1962/

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THOUGHT DISORDERS IN THE PARENTS OF SCHIZOPHRENIC PATIENTS: A STUDY UTILIZING THE OBJECT SORTING TEST*

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OL.
1
62/63

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THIS paper presents a replication of an experiment by MCCONAGHY[1] in which he found that sixty per cent of the parents of ten schizophrenic patients and at least one parent of each patient showed a disorder in conceptual thinking on the LOVIBOND version of the Object Sorting Test[2] in contrast to such findings in only nine per cent of parents of sixty-five controls. The findings suggest a dominant mode of inheritance of schizophrenia and hold great potential significance to the study of schizophrenia. LIDZ *et al.*[3] had previously drawn attention to the marked distortions in communicating and relating in each of the fifteen families of origin of schizophrenic patients they had studied intensively; in at least nine of these families one or both parents were either schizophrenic or paranoid, and in the remainder the aberrations in the parents' ways of thinking and relating could have undermined their offsprings' foundations in reality testing and rational thinking. The high incidence of psychotic and borderline disorders in these parents, none of whom had been hospitalized for them, suggested that focusing upon proclivities to symbolic distortions in family members rather than upon the incidence of manifest schizophrenia might further the study of the genetics of schizophrenia. McConaghy's procedure appeared to offer a simple and useful approach to the study of a critical aspect of the thought processes in relatives of schizophrenic patients.

McConaghy followed an hypothesis promulgated by KALLMANN[4] that "the factor for schizophrenia, even though recessive, may sometimes be expressed in a merely heterozygous condition, but only to the extent of schizoid personality changes . . . Schizoid types may be either heterozygotes with little resistance to an intermediate expressivity of their single gene, or strongly resistant homozygotes." He sought a means of determining whether one or both parents of schizophrenics might not exhibit schizoid traits more commonly than a control population. LOVIBOND[2] had developed a scoring technique for the Object Sorting

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Test for conceptual thinking that had enabled him to obtain a numerical score showing a high correlation with clinical estimates of the severity of thought disorders in schizophrenic patients. Since Rapaport and his co-workers had found the Object Sorting Test useful in diagnosing schizoid personalities as well as schizophrenia,[5] McConaghy considered that Lovibond's technique might serve his purpose.

DESCRIPTION OF THE TEST

The test is administered according to Rapaport's instructions. The subject is confronted with thirty-three common objects such as tableware, smoking items, and toy objects. The test is divided into two sections. In the first section, the subject is presented with an object and is asked to place with it all of the other objects that belong with it. After he has completed the sort, he is asked, "Why do all of these belong together?" This procedure is carried out with seven different objects in turn. In the second part the examiner presents the subject with twelve different groupings of the objects in succession, each grouping having some different characteristic in common; that is, they are all tools, all red, all smoking materials, etc. Each time the subject is asked, "Why do all of these belong together?" The subject's verbal responses are recorded verbatim.

VOL.
1
1962/

Lovibond's scoring system

The rationale for Lovibond's scoring system is based upon a Pavlovian approach to the nature of schizophrenic thinking. Conceptual thinking requires an inhibition of inappropriate associational linkages. Normally, the context determines what is thought about and what is inhibited, but schizophrenic patients cannot inhibit inessential linkages and irrelevant material interferes with proper category formation. The scoring directions can be found in his paper and will merely be summarized here.

Lovibond confined his scoring procedure to giving scores to responses that indicated inappropriate or inessential linkages, neglecting other aspects of the test performance. He distinguished eight categories of pathological responses, four of which Rapaport had found useful indicators of thought disorders, and added four new categories which might be considered as variants of Rapaport's categories. He quantified the procedure by giving a score ranging from 1 to 3 for each pathological response according to the extent of its abnormality using criteria provided in his article. The total score is the sum of the scores on the nineteen items; thus the possible range of scores is from 0 to 57.

The abnormal types of categorizations that occur most frequently are: *syncretistic* responses in which the subject groups objects together for a reason that does not explain why other objects are excluded; as "because all are useful," or "all exist"; in *fabulated* responses the subject groups on a concrete, temporal basis by winding a story around them; as explaining the grouping of a ball, eraser, and toy cigar by saying, "The man plays ball, then while smoking a cigar, writes a letter and uses the eraser"; in *chain* responses, the objects are united by a chain of linkages in that the second object shares an attribute with the first, the third with the second but not the first, etc., as when a rubber cigar is placed with the ball because both are rubber, but then matches are added to light the cigar. The remaining five categories occur less frequently. They are: *symbolic* responses where the

grouping is formed purely on a symbolic basis, as when a large and small fork are grouped together because "they are father and son"; *arbitrary* responses and *personal* associations that are variants of fabulatory responses; *irrelevant* responses that are a type of syncretistic response; and *impersonal* associations which include clang associations such as, "this is red and this can be read."

Lovibond, on the basis of his study of forty-five controls and thirty-two schizophrenic subjects, considered a total score of 7 or higher to be indicative of a schizophrenic thought disorder, but found that 9 per cent of the controls had scores above 6 and 34 per cent of his schizophrenic subjects had scores below 7.

McConaghy's experiment

McConaghy selected schizophrenic patients who obtained pathological scores on the procedure, considering that not all schizophrenic patients suffer from a thought disorder. He then tested both parents of ten of them, and compared the results with a control group of sixty-five subjects composed of Lovibond's forty-five controls plus twenty older patients in a general hospital, randomly selected. His results with the parents of the schizophrenic patients are presented in Table 1.

TABLE 1. MCCONAGHY'S SCORES OF PARENTS OF SCHIZOPHRENICS WITH "THOUGHT DISORDER" ON SORTING TEST

Patient	Mother	Father
1	7	0
2	7	16
3	10	0
4	14	2
5	3	14
6	0	8
7	4	10
8	11	9
9	0	10
10	6	13

It will be noted that twelve of the twenty parents or 60 per cent had scores of 7 or higher, and that at least one of each set of parents had a pathological score. Six of the sixty-five controls or 9·1 per cent had scores above 6. The results are significant by X^2 test at the 0·001 level.

McConaghy considered that finding a "score indicative of schizoid features in at least one of the two parents of every patient investigated would support Kallmann's concept — that the presence of a gene producing schizophrenia may be indicated in those people who successfully resist the disease by the production of a 'schizoid' personality. The finding that the significant score was present in one parent in all cases, but in both only twice might suggest a dominant rather than a recessive mode of inheritance. If confirmed, the discrepancy with Kallmann's conclusions might be explained by the homogeneous nature of the schizophrenic patients investigated, only those with clinical 'thought disorder' being selected."

Confirmation of McConaghy's results would not be sufficient to demonstrate the value of the procedure as a test for schizophrenia or for a thought disorder in parents that might predispose offspring to schizophrenia. Patients with other psychopathological conditions and their parents as well as populations in various intelligence ranges and socio-economic levels would have to be tested. However, an experiment of elaborate design did not seem warranted before obtaining a confirmation of McConaghy's results.

PROCEDURE

In the replication experiment McConaghy's procedure was altered in several ways: (1) Hospitalized schizophrenic patients who showed a thought disorder both clinically and on projective tests rather than patients with high Lovibond scores were selected, and they and their parents were tested. (2) Twenty-one pairs of parents formed the control series since parenthood itself might influence the test and because data were needed on the percentage of such couples which contained at least one member with a pathological score. (3) The reliability of the scoring of the psychologist who administered the test was checked by having a second psychologist score blindly; that is, neither knowing whether the subject belonged to the experimental or control series nor the marital pairings. (4) The vocabulary sub-test of the Wechsler Adult Intelligence Scale was administered to each subject to afford some indication of whether intellectual endowment affected the Object Sorting scores appreciably. Uncorrected scaled scores were utilized. The measure would not be thorough but it appeared essential to limit the testing, and the vocabulary test has a high correlation with the total WAIS score and is affected minimally by psychotic disorders.

Both patient and control groups had relatively high educational backgrounds. The control families, found with difficulty, were provided by three churches of different denominations and were otherwise unselected except to ascertain that neither parents nor any of their children had ever been clinically psychotic. The age range of the control parents was lower than the patients' parents (Table 2); but a correlation of only 0·15 between age and the (revised) test scores indicated that age did not influence the scores significantly. Years of education and vocabulary scores of the control and experimental series showed no significant differences (Table 2). The mean of both groups had approximately four years more schooling than McConaghy's and Lovibond's subjects; a difference that may relate to cultural factors, since McConaghy worked in England and Lovibond in Australia.

TABLE 2. AGE, EDUCATION AND VOCABULARY SCORES OF EXPERIMENTAL AND CONTROL GROUPS

			Age		Years Education		Vocabulary Scores	
		No.	Mean	SD	Mean	SD	Mean	SD
Experimental Group	Patient	10	24·3	3·13	14·1	2·13	14·3	2·16
	Father	10	58·9	5·74	14·6	3·27	13·1	2·60
	Mother	10	54·0	4·42	13·3	3·02	14·6	2·40
Control Group	Father	21	47·5	4·89	15·1	3·34	13·8	3·06
	Mother	21	45·9	5·62	13·7	3·24	13·4	2·40

VOL. 1 1962/

First trial

Using test protocols that were not included in the experiment, two psychologists worked out a scoring system according to the instructions in Lovibond's article. Then, scoring the tests independently, they achieved a reliability coefficient of 0·90. As the experiment clearly failed to confirm McConaghy's findings, the data will not be presented in detail. Only five of the twenty parents in the experimental group in comparison with twelve of the twenty in McConaghy's series had scores of 7 or higher. As 11·9 per cent of the control parents had scores above this cutting point as compared to 9·1 per cent of McConaghy's controls, it appeared that the interpretation of the scoring procedure had been reasonably correct.

Despite the failure to obtain significant results, a definite impression was gained from this first trial that clear-cut differences existed between the test protocols of the experimental and control subjects that the scoring procedure had missed. Protocols not used in the experiment were sent to Lovibond for scoring and comment on scoring criteria. Lovibond tended to give higher scores for faulty groupings, and, in addition scored faulty responses that subjects retracted. He also had found in recent work that about 20 per cent of controls rather than 9 per cent scored 7 or higher.

The psychologists modified the scoring technique and rescored the protocols. The new results were in close agreement with McConaghy's except that 19 per cent of the controls in contrast to 9·1 per cent of his controls had pathological scores. The results, however, could not be considered valid as both psychologists were "contaminated" by their previous work with the protocols.

Two new psychologists were trained in the revised scoring technique. Neither of the new scorers knew which were experimental and control subjects. They achieved a reliability of 0·94. The results given in Table 3 are the averages of their scores.

TABLE 3. SCORES OF PATIENTS AND PARENTS ON OBJECT SORTING TEST (REVISED SCORING)

No.	Patient	Father	Mother
1	9	6	5
2	13	5·5	7
3	6	4	7·5
4	5	35	19
5	9	5·5	5
6	1	6	7
7	12	17	3·5
8	10	9	16·5
9	9	11	1
10	17	1	2

Nine of the twenty parents of patients (45 per cent), four fathers and five mothers, had scores above the cutting point in comparison with eight of forty-two control parents (19 per cent), three fathers and five mothers (Table 4).

TABLE 4. NUMBER OF PARENTS OF PATIENTS AND CONTROLS WITH SCORES OF 7 OR HIGHER (REVISED SCORING)

	Below 7	7 or Higher	Total
Schizophrenics' parents	11 (55%)	9 (45%)	20 (100%)
Control parents	34 (81%)	8 (19%)	42 (100%)

$X^2 = 3{\cdot}37 \quad p < 0{\cdot}10$

Seven of the ten patients had at least one parent with a score of 7 or higher. There were no sets of control parents in which both the parents had a score above 6, so that 38 per cent of the control children had one parent with a score above the cutting point (Table 5).

TABLE 5. NUMBER OF PATIENTS AND CONTROL CHILDREN WITH AT LEAST ONE PARENT SCORING 7 OR HIGHER (REVISED SCORING)

	Below 7	7 or Higher	Total
Schizophrenic patients	3 (30%)	7 (70%)	10 (100%)
Controls	13 (62%)	8 (38%)	21 (100%)

$X^2 = 1{\cdot}63$ not significant

Thus, using the cutting point established by Lovibond, the results neither match McConaghy's findings of 60 per cent of parents of patients giving high scores in contrast to 9·1 per cent of his controls, nor are they statistically significant. However, abandoning the arbitrary cutting point and handling the data in other ways indicates that the series are decidedly different.

First, a median test was applied to the data; that is, the median for the combined experimental and control groups which is between 4·5 and 5 was used as the cutting point. The difference between groups is significant at the 0·02 level (Table 6).

TABLE 6. MEDIAN CUTTING POINT (REVISED SCORING)

	Low	High	Total
Schizophrenics' parents	5 (25%)	15 (75%)	20 (100%)
Control parents	26 (62%)	16 (38%)	42 (100%)

$X^2 = 5{\cdot}96 \quad p < 0{\cdot}02$

Second, the experimental and control series, as groups, were compared by the Mann Whitney U Test. The two series were combined into one distribution and given rank scores, 1 for the lowest and 62 for the highest. When the sums of rank scores for the two groups are compared the difference is significant at the 0·01 level.

VOL. 1 1962

Thus, although the experiment failed to confirm McConaghy's findings using the Lovibond cutting point, it yielded impressive evidence that the parents of these schizophrenic patients as a group have difficulties with conceptual thinking and category formation to a greater extent than the control parents. The trend is sufficiently firm and clear to warrant further attention to the hypothesis that schizophrenic patients frequently and perhaps always have a parent who suffers from a disorder in conceptual thinking.

There are several possible reasons for the differences between the results of this experiment and McConaghy's.

1. The interpretation of the scoring criteria may still differ. However, considerable experimentation went into seeking to score according to Lovibond's instructions and examples. Such experimentation may diminish the validity of the findings, but in this study we were primarily seeking to learn if McConaghy's results could be validated.

2. All patients whose parents composed McConaghy's experimental series had scores of 7 or higher on the test. McConaghy emphasizes the importance of this criterion for selection. Three patients in this experiment did not meet this criterion. However, all three patients with low scores had at least one parent with a score above the cutting point, and all three pairs of parents with low scores had schizophrenic offspring with high scores (Table 3).

3. McConaghy did not indicate whether the same person administered and scored the test nor offer data concerning the reliability of the scoring.

COMMENT

Even though the findings of the experiment were not as decisive as McConaghy's, they warrant entertaining the hypothesis that the presence of such thought disorders in a parent may be one essential factor in the appearance of schizophrenia in an offspring; or the alternate hypothesis that if neither parent has this type of thought disorder, it is unlikely that a child will become schizophrenic. It should be specifically noted that some individuals who perform well on this single test, will reveal aberrant thinking on other tests. Such hypotheses are worth testing carefully because procedures derived from them could provide a definite and measurable factor associated with the etiology of schizophrenia and could supply a much needed instrument for epidemiological studies. They are in accord with our clinical studies[6] which have shown that a multiplicity of difficulties exist in families with schizophrenic offspring but suggest that it may be the presence of a thought disorder in one or both parents that differentiates them from other seriously disturbed families. Whether the presence of such thought disorders in the parents indicates a genetic transmission as McConaghy assumes or an extragenetic environmental transmission remains a matter for speculation and study.

SUMMARY

A replication was carried out of an experiment in which McConaghy, using the Lovibond system for scoring the Object Sorting Test, had found that 60 per cent of the parents of ten schizophrenic patients and at least one parent of each patient in contrast to but 9·1 per cent of sixty-five controls had scores of 7 or higher, a level Lovibond considered indicative of a schizophrenic thought disorder. These results suggested consideration of a dominant genetic transmission of schizophrenia.

The replication experiment employed "blind" raters who achieved high reliability. The initial attempt failed to confirm McConaghy's findings, but when the scoring criteria were altered in accordance with Lovibond's instructions and new raters used, 45 per cent of the twenty parents of ten patients compared with 19 per cent of forty-two control parents had scores of 7 or higher; and 70 per cent of the patients and 38 per cent of the control children had at least one parent with a score above the cutting point. These differences between the series were not significant. However, using a median cutting point instead of Lovibond's cutting point, the difference between the series was significant at the 0·02 level, and when the sums of the rank scores for the two series were compared by the Mann Whitney U Test, the difference was significant at the 0·01 level.

The results indicate that parents of schizophrenic patients show difficulties in conceptual or categorical thinking more frequently than control parents, and warrant efforts to refine further the ability to differentiate parents of schizophrenic patients from controls by means of the Object Sorting Test.

VOL.
1
1962/

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BIOELECTRIC CORRELATES OF HYPNOSIS: AN EXPERIMENTAL REEVALUATION*

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OL.
1
62/63

THERE is a long history of research on the physiology of hypnosis. One major goal of this work has been to obtain insight into the nature of the hypnotic state, particularly in relation to sleep and other states of consciousness. An additional goal has been to discover some reliable and objective indicant of the presence and, if possible, depth of hypnosis. Recent reviews of the field, however, agree that the results to date of these investigations have been singularly disappointing.[1–4]

In contrast, findings which appear to be more promising have been reported in a series of papers by RAVITZ.[5–12] Changes in electrical potential recorded from the head during hypnosis were reported to offer a reliable measure of trance depth.

These results are of particular interest since electrodes placed on the head might well be assumed to be recording bioelectric potentials† originating in the brain. Indeed, at least one author has made this assumption and has consequently stated that "Cortical DC standing potential is directly correlated with incidence and with depth of hypnosis".[14]

There are reasons for caution, however, in drawing the conclusion that these potentials are of cortical origin. One electrode was always placed on the head and served as the active electrode. The largest potentials were found when the palms were used as the reference placement. The palms are known to be very active psychic sweating areas and are indeed the area of preference for recording galvanic skin response (GSR) changes.

It is therefore quite possible that local changes in level of palmar potential contributed to the changes recorded during hypnosis. The fact that smaller shifts were found when the reference electrodes were placed on the chest rather than on the palm suggests that palmar

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†The word "potential" will be used throughout this report to mean "electrical potential" and not in any other sense. It should be kept in mind that we are not concerned in this study with the skin potential measure of the GSR as it is usually defined: a momentary change in skin potential in response to stimulation, such as an electric shock or loud sound. It is the ongoing level of skin potential which is the object of this investigation. As has been pointed out by WOODWORTH and SCHLOSBERG[13], the baseline, or ongoing level of skin potential, has no special name. Investigators have been more concerned with changes in level than in ongoing level.

potentials were contributing to the effects observed. The palmar reference electrode might well have been over an area as physiologically active as (or even more active than) the area under the head electrode.

Evidence for changes in ongoing level of skin potential at the palms would be of great theoretical interest in its own right, since the level of bioelectric activity of the palms has been widely regarded as one of the best peripheral measures of the level of activation of the central nervous system.[15]

In view of the foregoing considerations as well as the possible major implications of Ravitz's findings, it was decided to attempt to replicate his work and to explore the nature of the bioelectric changes found. The purposes of this investigation were (1) to determine the magnitude and reliability of changes in potential during hypnosis and (2) if reliable changes were found, to determine whether they originate from the head, from the palms, or from both locations.

VOL.
1
1962/

PROCEDURE AND METHODS

Subjects

Six undergraduates who had previously been selected as excellent hypnotic subjects were used. In all cases, they had had previous experience as subjects in hypnotic experiments and in three cases (Subjects *A*, *C* and *E*) had had experience in experiments involving physiological recording as well. Excellent hypnotic subjects were used in order to maximize any physiological changes associated with hypnosis, particularly if such changes were a function of depth of hypnosis. In addition, it was desirable to use subjects who showed no anxiety about entering hypnosis, since changes in ongoing level of palmar potential are known to occur in situations which produce anxiety. Insofar as possible, attempts were made to reduce any anxiety associated with the physiological recording conditions. It was carefully explained to the subjects that no external current would be imposed on them and that only the current that their skin itself naturally produced would be recorded.

Electrode system

It is essential in DC recording to use an adequate electrode system. The electrodes must be drift-free and introduce negligible bias potentials into the system being studied. Silver–silver chloride sponge electrodes that fulfil these requirements have been described elsewhere.[16,17] These were modified for use on the head.[18] The bias potential of the electrode pairs was less than 0·05 mV, which is negligible at the level of recording used.

Recording apparatus

Recordings were made on a transistorized Offner Type R 8-Channel Dynograph. The input impedance of this amplifier at the gain used is 1 meg, with 1μV/hr equivalent pen drift at maximum sensitivity under normal ambient conditions. A uniform gain of 10 mV/cm was used, with a paper speed of one cm/min. This slow paper speed has the advantage of allowing one to view an entire recording of a hypnotic trance period within a length of recording paper short enough to allow analysis by visual inspection.

Recordings were made with the subject in a Barca-Lounge chair, sitting in a shielded room adjacent to the control room. The ambient noise level was low, and the experimenter

communicated with the subject through an open door between the two rooms. Overhead lights in the room were left on.

Electrode placements

Three electrode placements were used:

Placement 1: Head–Palm. Ravitz reported that either the right or the left temporal areas could be referred to either palm with equivalent results. In order to have recordings from these placements that were comparable to the continuous recordings made by Ravitz, two temporal placements (right and left) were combined in parallel as active areas, and right and left palmar areas were similarly combined as reference areas. Placement 1 was thus recording bilaterally with the temporal regions active in reference to the palms (in terms of direction of input coupling).

OL.
1
62/63

Placement 2: Head–Chest. In order to make continuous recordings comparable to the spot determinations of Ravitz, right and left temporal placements were combined in parallel as active in relation to two electrodes on the right and left mid-clavicular lines which were combined as reference points.

Two temporal electrodes were used on each side of the forehead to allow simultaneous recordings from the head–palm and head–chest placements. The same temporal electrodes could not, of course, be referred to both the chest electrodes and the palm electrodes at the same time. Such an arrangement would not have been physically equivalent to separate placements from head to chest and from head to palm. Therefore two electrodes were used on each side of the head: one pair (A) more medially placed than the other pair (B). For three subjects, the order of the pairs serving as active electrodes for head–palm recording was ABBA; for the other three subjects, the order was BAAB. It was not expected that Pair A and Pair B would differ significantly in activity, and this proved to be the case.

Placement 3: Palm–Arm. This is the standard placement used in our laboratory for recording GSR activity. The active electrode is on the thenar eminence of the palm and the reference electrode on a dorsal point on the forearm 10 cm above the styloid process. A unilateral placement was used on the right side.

From extensive experience, this forearm placement has proven to be an area of minimal GSR activity, quite suitable for reference purposes. Preliminary recordings between it and the mid-clavicular areas used indicated that they too were areas of minimal activity and therefore also suitable reference areas.

Before continuing, a word should be said about the choice of which electrodes would serve as "active" electrodes and which as "reference" electrodes. If changes in potential during hypnosis are cortical in origin, it would be reasonable to assign the head electrodes as "active". This was done for both Placements 1 and 2. The palm was assigned as "active", however, in Placement 3, since this is our standard recording procedure. When considering the apparent polarity of recordings it must be kept in mind that in the one instance (Placement 1) the palm serves as the reference area while in the other instance (Placement 3) the palm serves as the active area.

When electrodes are placed on two areas of the body, the potential recorded from them is the difference in voltage between the local voltage level of each area. Whether this difference is recorded as negative or positive depends entirely upon which electrode is

arbitrarily assigned as the "active" electrode and which as the "reference" electrode, that is, into which input terminals of a differential amplifier they are plugged.* The actual physical polarity must be determined by previous calibration from a known physical source. Therefore a local increase of 10 mV under the "active" electrode would produce the same apparent change in the record as a local decrease of 10 mV under the "reference" electrode. In order to be able to attribute an apparent change in a recording to a local change at the "active" electrode rather than to a local change of equal magnitude but opposite polarity at the "reference" electrode, one must know with reasonable certainty that the area under the "reference" electrode is not undergoing any significant voltage changes during the recording period.

Instructions and Hypnotic Induction Procedure

All subjects had had previous experience with a variety of hypnotic induction procedures and had developed the ability to enter deep hypnosis readily. In order to reduce any residual anxiety they might have had about the recording situation, subjects were shown the electrodes and told that some physiological measures would be taken while they were awake and while they were in hypnosis. The exact nature of the activity being studied was not explained. Most subjects thought that electroencephalograms were being taken. Each hypnotic period lasted a minimum of 4 min with a minimum of 2 min both before and after. There were four such hypnotic periods, each of which will be referred to as a *sample*. Induction was begun by counting from 1 to 10, and hypnosis was terminated by a count from 10 to 1. Simple suggestions of relaxation and deepening of hypnosis were made repetitively. Any suggestions of "sleep" were deliberately not given. It has been shown by BARKER and BURGWIN[19,20] that sleep can be superimposed on hypnosis by such suggestions, and such a confusion of states was certainly not desired.

The subject's role was entirely passive during hypnosis. Preliminary tests had shown that any specific suggestion, such as an auditory hallucination or arm immobilization, tended to decrease the shift in potential occurring during hypnosis. Suggestions of amnesia and a simple posthypnotic suggestion were made each time just before the termination of hypnosis. Amnesia and the posthypnotic suggestion were tested after each hypnotic induction. Hypnosis was induced four separate times for each subject, always during the same recording session. About a quarter of an hour intervened between samples, and the entire recording session lasted some 3 hr.

RESULTS

Form of the response

Three typical records are reproduced in Fig. 1. Shifts in level in the head–palm and palm–arm placements during hypnosis are large and apparently similar in size, although

*The terms "active" and "reference" as used here are merely the names of the two electrodes used. We are concerned with the distinction between lead polarity and apparent polarity, which is entirely a function of input coupling direction. Obviously, naming an electrode the "active" electrode does not guarantee that the area upon which it is placed is in any way more active physiologically than is the area under the electrode named the "reference" electrode. Whether an area of skin is electrophysiologically active or inactive is an intrinsic property of the skin itself and quite independent of the presence or absence of an electrode.

VOL. 1 1962/

opposite in direction; whereas changes in the head–chest placement are slight by comparison. Note the rapid return of the ongoing level at the termination of hypnosis. This is typical and often quite dramatic. Note also the relative smoothness of the record during hypnosis compared to the waking periods. Further investigations of this phenomenon, which will be reported in detail elsewhere, have shown that such records are readily repeatable and that the shift in level and the smoothing of ongoing activity occur together during hypnosis.

OL.
1
62/63

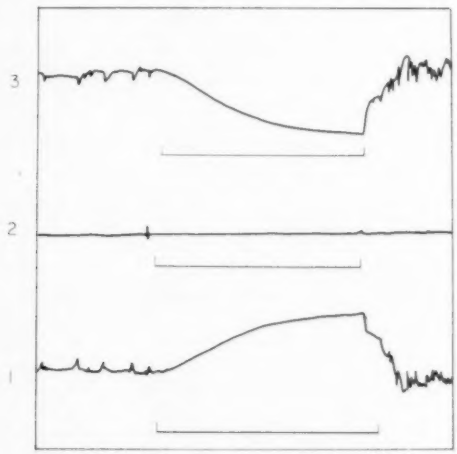

FIG. 1a

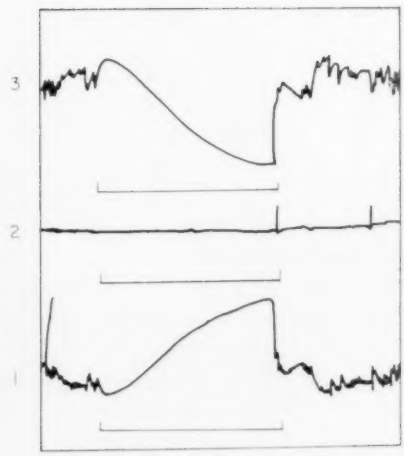

FIG. 1b

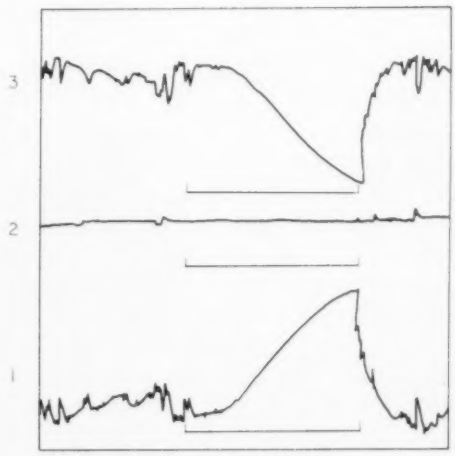

FIG. 1c

FIG. 1. Three typical records from three different subjects of changes in ongoing level of skin potential recorded from the following placements: (1) head–palm, (2) head–chest, and (3) palm–arm. The duration of hypnosis is marked by the heavy line under each record.

Correlation between head–palm and palm–arm activity

The consecutive simultaneous measurements* made on the records from the head–palm and palm–arm placements were correlated for each subject for each of the four periods during which hypnosis was induced.

If the hypothesis is made that local palmar changes in skin potential are alone responsible for the shifts recorded for the head–palm as well as the palm–arm placements, one would expect these two records to be highly correlated. One would also expect the direction of correlation to be negative, since in only one instance is the physiologically active palm area used as "active". Records from these two placements should be mirror-images of each other.

This is indeed the result. Individual product-moment correlations for each sample are presented in Table 1. The coefficients range from −0·926 to −0·998. All of these correla-

TABLE 1. PRODUCT–MOMENT CORRELATION COEFFICIENTS BETWEEN PALM–ARM AND HEAD–PALM PLACEMENTS

Subject	Sample 1		Sample 2		Sample 3		Sample 4	
	r	*n*	*r*	*n*	*r*	*n*	*r*	*n*
A	−0·986	30	−0·983	35	−0·988	31	−0·983	31
B	−0·954	32	−0·990	34	−0·996	42	−0·986	38
C	−0·967	29	−0·926	35	−0·984	33	−0·955	33
D	−0·966	37	−0·984	37	−0·993	35	−0·986	38
E	−0·976	35	−0·984	35	−0·981	37	−0·960	34
F	−0·994	30	−0·994	32	−0·998	37	−0·989	31

Correlation coefficients of consecutive simultaneous measures of recordings from the palm–arm and head–palm placements. The numbers under the columns headed *n* indicate the number of measurements made on each sample. This number varies because the exact duration of the samples varied somewhat.

tions obviously are significant far beyond the $p=0{\cdot}001$ point. In every instance, the correlations are as predicated.

These results indicate that both placements are essentially recording the same physiological event. Since only the palmar area is common to both placements, this physiological event must be taking place locally on the palms.

It should be remembered that the correlation coefficient is a nondimensional quantity. That is to say, either of two variables being correlated may be multiplied or divided by a constant or, indeed, undergo any linear transformation, and the numerical value of the coefficient of correlation will remain constant. A correlation coefficient, therefore, gives no information about the relative magnitudes of the variables being correlated but only measures the degree of linear association between them. In order to evaluate the relative contribution in terms of magnitude of the various placements used, the relative sizes of the changes observed must be compared.

*Statistical analysis of the records was done from numerical reduction of the recordings made with a Benson-Lerner Oscar Model J Data-Reduction System. Readings were made at points 0·25 sec apart with four readings in the prehypnotic interval and eight readings in the posthypnotic interval. The number of readings during hypnosis varied with the exact duration of each sample.

VOL. 1 1962/

Comparison of maximum magnitudes of shift

The maximum magnitudes of change in level of skin potential during hypnosis of all subjects appear in Table 2. In each instance the magnitude of maximum shift for the head–palm

TABLE 2. MAGNITUDE OF MAXIMUM CHANGE IN POTENTIAL LEVEL DURING HYPNOSIS

Subject	Sample 1	2	3	4
Placement 1: Head–Palm				
A	−21·3	−25·0	−34·7	−31·9
B	− 6·3	−12·3	−10·7	−10·0
C	−26·1	−21·6	−28·8	−13·2
D	6·6**	− 7·0	−18·0	−19·4
E	−19·3	−16·4	−15·2	−15·1
F	−20·9	−23·7	−21·4	−17·4
Placement 2: Head–Chest				
A	0·8	− 0·3	− 0·1 0·5	0·2
B	− 0·5 0·5	− 0·5 0·5	− 0·6	− 0·1 0·4
C	4·8*	0·2	− 0·1	0·0
D	6·1**	2·8	1·1	− 0·2 0·8
E	− 0·3	− 0·4	0·5	1·1
F	1·1	0·5	0·1	0·3
Placement 3: Palm–Arm				
A	24·4	22·5	32·5	31·7
B	6·0	11·3	9·5	9·7
C	20·1	16·8	25·4	12·2
D	− 5·8**	9·2	16·1	16·4
E	16·9	17·1	16·6	16·1
F	21·5	25·1	25·6	26·0

*Atypical record: artifact. **Atypical record: initial anxiety.

Maximum change in level of skin potential during hypnosis from the initial waking level just prior to the beginning of the hypnotic induction. All values are shown in mV. Sample 1 of Subject *D* is not a typical record, since the usual shift in level is confounded by the subject's initial anxiety. The recording from the head–chest placement on Sample 1 of Subject *C* shows a sudden change in level due to an artifact.

and palm–arm placements is approximately equal and of opposite polarity. This is exactly the result to be expected if the shifts observed during hypnosis were due only to local changes under the palmar electrodes. A Wilcoxon Matched-Pairs Signed-Ranks Test[21] shows no significant difference between the two placements. These results, as did the results of the correlational analysis, further confirm the hypothesis that the head–palm and palm–arm placements are recording the same physiological event occurring locally on the palms.*

*As WILDER[22] has pointed out, the magnitude of a physiological response is often a function of the initial level of ongoing activity prior to the response. Plotting of our data led us to suspect that magnitude of change was highly correlated with initial level. Using mean initial levels and mean maximum shifts during hypnosis (averaging the four samples together for each subject), a rank order correlation coefficient was found of $r_S = -0{\cdot}86$ (significant at the $p = 0{\cdot}05$ point).

Two samples were atypical, although for purposes of data analysis they were included as they appeared objectively. In the first, Sample 1 of Subject *C*, an artifact appears in the channel recording from the head–chest placement. On the record this appears as a sudden deflection of this one pen, which does not return. The second anomalous record is of interest in its own right. This is Sample 1 of Subject *D*, a female undergraduate who had not previously taken part in any experiments involving physiological recording. Although efforts were made to reduce anxiety for all subjects, she was unsure that the procedure was really safe. After the first sample, she volunteered the information that she had been somewhat anxious. Looking at this record (Fig. 2a), one sees what would appear to be a typical

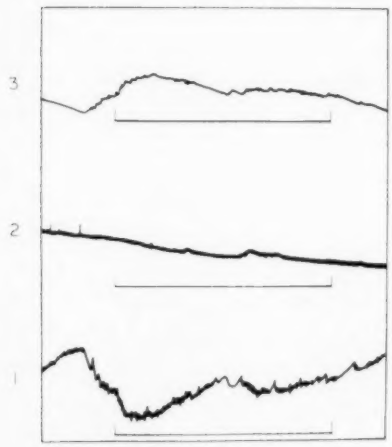

FIG. 2a

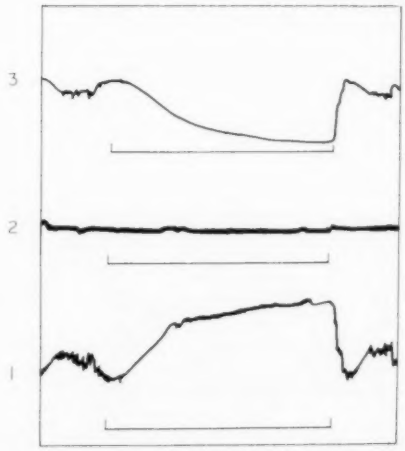

FIG. 2b

FIG. 2. Two records from Subject *D*, who reported initial anxiety in the recording situation. The first (2a) is the first sample taken and shows the effect of her anxiety. The second (2b) is a record taken approximately one-half hour later, when she reported that she was no longer anxious. The record now appears typical.

shift during hypnosis embedded in a general shift toward the opposite direction. Her subsequent records during this experimental session are all typical (Fig. 2b), and indeed so were all her records on later occasions. (Preliminary investigations with other subjects with varying degrees of initial anxiety had shown similar initial records.)

Analysis of head–chest activity

The head–chest placement gave small erratic shifts, some in one direction, some in the opposite direction, and some with maxima in both directions. There were brief initial shifts in the records of three subjects. In order to make the maximum shift readings comparable for all three placements, this period was not included in determining the maxima for head–chest placement, since it had not been included in determining maxima for the other placements. The shifts shown are, in most cases, within the order of magnitude of random changes in the resting subject, with the exception of the two anomalous records described above.

Group summary data are presented in Table 3. Here there is very good agreement between the magnitude of the shift of the head–palm and palm–arm placements. The mean head–chest placement is negligible in comparison. Some electrodermal activity may be present at the temples, although individual differences in the pattern of distribution of the

TABLE 3. GROUP SUMMARY DATA

Placement	Mean (in mV)	S.D. (in mV)
Head–Palm	−17·88	±8·94
Head–Chest	+ 0·66	±1·50
Palm–Arm	+17·62	±8·65

The means and standard deviations of the maximum change in level of skin potential during hypnosis averaged over all subjects and all samples.

OL.
1
62/63

sweat glands are great in the facial areas.[23] If this is an area of psychic sweating, some slight shifts might be expected from the head–chest placement, for in both this placement and in the palm–arm placement, the area under the "active" electrode would be an electrodermally-active area. The mean value found, +0·66 mV, is in the direction predicted by such an hypothesis. However, the relatively large contribution made by the two anomalous samples should be taken into account. If these are omitted, the mean shift for this placement falls to +0·37 mV. This value is also in the direction predicted. A one-tailed *t*-test based on subject means (omitting the two anomalous samples) shows that this mean shift differs significantly from zero at the $p=0{\cdot}05$ point ($t=2{\cdot}33$, $df.=5$).

In addition to the small size of these shifts, the fact that maxima occur in both the positive and negative directions (sometimes even in the same sample) suggests that activity from the head–chest placement may also be due in part to small random fluctuations in level rather than be only a miniature reflection of palmar changes.

DISCUSSION

These results demonstrate that there are large and reliable changes in basal palmar skin potential associated with hypnosis. These changes are the first reproducible physiological alterations that we have observed to accompany hypnosis despite several years of extensive exploratory investigations of physiological changes during this state.

The evidence strongly suggests that the shifts in bioelectric potential previously reported by Ravitz were predominantly palmar rather than cortical in origin. We do not want to negate the possibility that there may be changes in cortical steady potentials during hypnosis. The available evidence would lead one to expect that such changes would probably be well below the order of magnitude of the changes found here. If so, they would be undetectable at the level of amplification used in the present study.

There are few reports in the literature concerning such potentials. The work of KÖHLER and his co-workers[24–26] provides an example. In these studies maximal changes in steady

potential originating in the visual and auditory sensory cortex of the order of magnitude of 20–50μV were observed. There are technical difficulties in recording brain potentials through the intact head, not the least of which is unequivocally identifying the potentials found as actually originating in the brain. The assumption that these potentials were cortical in origin was supported by the fact that they showed congruence with known anatomical locations of the cortical areas involved. This assumption was further corroborated at a later date by direct recording from the exposed cortex of the cat.[27–31] To demonstrate convincingly that any potential changes recorded from the intact head during hypnosis were of intracranial origin would be exceedingly difficult. Hypnosis as it is commonly viewed in humans is a phenomenon which requires symbolic communication and does not seem to be analogous to so-called "animal hypnosis".[32] Thus, no direct analog is available for animal research. Ultimately, investigations conducted in conjunction with neurosurgical procedures may be necessary to show convincingly the presence or absence of cortical potentials correlated with hypnosis.

VOL.
1
1962/

While the possibility of cortical changes during hypnosis remains open, and a fascinating issue for further inquiry, there is little doubt that the potential changes reported by Ravitz with head–palm placements should be attributed to local changes in potential on the palms.

These alterations in palmar potential are of major significance, however, in their own right. Exploratory investigations under a variety of hypnotic induction procedures have continued to demonstrate the characteristic changes reported here.

These exploratory investigations, involving about 120 subjects in all, have shown that relaxation is not a necessary condition for the appearance of increased palmar potential during hypnosis. Identical records were obtained during waking hypnosis and during hypnotic suggestions of general excitement and tension. In neither condition was muscular relaxation produced. Autohypnosis with or without the eyes closed produced similar shifts in level. Spontaneous day-dreaming also produced similar shifts. A detailed report of the effects of these and other relevant parameters and a comparison with other, nonhypnotic conditions that produce similar changes is in preparation.

The final interpretation of skin potential alterations associated with hypnosis must await further investigation. In particular it will be necessary to determine under what other conditions such changes take place. It is tempting none the less to speculate on the significance of the increase in palmar potential during hypnosis.

Level of palmar electrodermal activity has been widely used as a peripheral indicant of central activation.[33] Palmar conductance, for example, has been shown to parallel changes observed during sleep in 2–4 cps and 8–12 cps components of the EEG activity spectrum.[15] More recently, VENABLES and KING[34] have reported a correlation of −0·79 between palmar skin potential and the two-flash threshold in waking subjects. These authors used the two-flash threshold as a central measure of brain stem reticular formation activation on the basis of changes in two-flash threshold and critical fusion frequency in response to direct electrical stimulation of the reticular formation reported by LINDSLEY[35] and by JUNG.[36]

The marked increase in palmar potential which occurs during hypnosis may then be interpreted as indicating an increase in level of activation during hypnosis over that found in the normal resting state. This would imply that the hypnotic subject, even though he

may appear completely passive and relaxed, is in a state of increased attention and arousal.

This interpretation is consonant with previous EEG studies which have found the pattern of EEG activity during hypnosis to resemble that of waking subjects rather than that found in sleep.[1–4] The increase of palmar potential also indicates that the hypnotized subject is not in a state resembling sleep but instead resembling highly alert wakefulness.

This interpretation also agrees with the traditional view that hypnosis is a state of heightened motivation and increased attentiveness. In addition, the fact that there is a marked smoothing of ongoing potential may well indicate that the normal fluctuations of attention found during waking relaxation have been replaced by the highly focused state of attention traditionally assumed to be a condition of successful trance induction. LEVY *et al.*[37] have recently reported a smoothing of palmar skin resistance "during long periods of concentration in which the subject 'insulates' himself from external stimuli."

Additional direct evidence that hypnosis is a state of high activation should be found before further implications of such interpretation are made. These speculations, while consistent with a number of observations, will need to be validated by specific studies before further conclusions are drawn. They are proposed as heuristic hypotheses which may facilitate further research into the neurophysiological bases of the hypnotic phenomenon.

OL.
1
62/63

SUMMARY

The findings of the present study may be summarized as follows:

(a) Previously reported bioelectric changes were found to be palmar in origin.

(b) No evidence was found to indicate the presence of cortical potential changes during hypnosis. However, the question of the existence of such changes must at present remain open.

(c) Large and reliable changes in palmar potential level were observed during hypnosis. These changes were: (1) an increase in level of palmar potential of the order of magnitude of 10–30 mV, the increase in level shifting gradually and returning (usually) dramatically to previous levels at the termination of hypnosis, and (2) a marked smoothing of ongoing activity.

(d) These changes are most striking when only general suggestions of deepening hypnotic trance are made, specific suggestions tending to decrease the level of potential.

(e) These findings are tentatively interpreted as indicating that the hypnotic state is a state of increased central activation and focused attention. The level of arousal is not that found in sleep but rather that found during highly alert wakefulness.

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VOL. 1 1962/

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OL.
1
62/63

VOL.
1
1962/

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CHROMATOGRAPHIC STUDY OF "REIGELHAUPT" CHROMOGENS IN URINE*

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OL.
1
62/63

CONSIDERABLE neurochemical and pharmacological evidence has accumulated suggesting a relationship between indole metabolism and mental illnesses such as pellagra, Hartnup's disease and phenylketonuria. Recently these studies have been extended to schizophrenia with encouraging but inconclusive results. Among the many findings is the discriminatory test proposed by REIGELHAUPT[1] who observed a marked incidence of "positive" Hopkins Cole reactions among urines from schizophrenics. Although others have confirmed these results we were unable to do so in a previous study,[2] when schizophrenic and non-schizophrenic subjects were identically maintained in respect to diet, medication and ward environment. Rather, a preponderance of positive reactions was obtained on subjects in both groups.

The Reigelhaupt test consists of the formation of violet chromogens at the interface between sulfuric acid and a mixture of glyoxylic acid, urine and copper sulfate. Because it is conceivable that our experimental conditions introduced "spurious" chromogens masking the "true" chromogens, the present study was undertaken to explore the nature of the contributory compounds. The relationship of chromogens to diagnosis, urinary toxicity, and "abnormal" aromatic amino acid metabolism was also examined. To this end the Reigelhaupt test was adapted for chromatographic use and applied to: whole urine concentrates; *n*-butanol extracts which reportedly concentrate Reigelhaupt chromogens[3]; extracts of charcoal treated urines producing differential toxicity to mice[4]; butenone-2-extracts reportedly containing differential quantities of 6-hydroxyskatole sulfate[5]; and urine concentrates from subjects receiving phenothiazine medication.

The results obtained will be discussed with regard to the apparent significance of 6-hydroxyskatol sulfate, Mauve factor, Depression factor, and bufotenine in urine, as well as to the nature of Reigelhaupt chromogens.

METHOD

Subjects were drawn from the population of the Ypsilanti State Hospital upon unanimous diagnostic agreement obtained independently by three psychiatrists. The subjects were maintained on a constant repetitive diet with vitamin supplements throughout the course

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of the study. Medication was discontinued two months before initial testing and reinstated after test completion when drug studies were carried out. Urine concentrates of a total of 40 schizophrenics (24 chronic undifferentiated, 1 simple, 1 hebephrenic, 9 paranoids, and 5 type uncertain) and 17 non-schizophrenics (5 non-psychotic chronic brain syndromes, 8 sociopaths, 3 alcoholics, 1 psychotic brain syndrome) were examined for Reigelhaupt chromogens. Butanol extracts were prepared from the urines of 5 schizophrenics (chronic undifferentiated); concentrates of urinary toxic factors from 2 non-schizophrenics (sociopaths), 5 schizophrenics (2 paranoid and 3 chronic undifferentiated), and 3 subjects of uncertain diagnosis; butenone extracts, from 18 schizophrenics (9 chronic undifferentiated, 7 paranoid, 2 type uncertain) and 8 non-schizophrenics (5 sociopaths, 3 chronic brain syndrome); and concentrates from subjects on phenothiazines, from 5 schizophrenics (3 paranoid and 2 chronic undifferentiated).

VOL.
1
1962/

Specimens

Urines were collected over a twenty-four hour period and refrigerated between collections. Aliquots of the twenty-four hour urine were either used immediately or stored at −15°C. The Reigelhaupt test was carried out in the manner previously described, using mixtures of copper sulfate and glyoxylic acid.[2,6] In some studies, only samples giving clear positive tests at the time of preparation as well as at the time of initial collection were chromatographed, so as to minimize decomposition of abnormal chromogens.

Procedures

Samples of whole and treated urine were concentrated either by lyophilization or by reduced pressure evaporation in a flash evaporator at a bath temperature of 40°C. Both methods gave identical chromatographic results. Precipitate formed during evaporation was left in contact with the concentrated liquid and chromatogrammed, either by dabbing onto the origin or by application after solution in acetone-water. Chromatograms were spotted in quadruplicate; each spot containing the equivalent of 0·5–10 ml of initial urine, depending upon the experiment and the sample used. Comparisons between diagnostic groups were carried out using that amount of concentrate containing 0·50 g of creatinine.

Butanol extracts were prepared by shaking 100 ml of acidified whole urine with 50 ml of *n*-butanol, centrifuging and concentrating. The method of SPRINCE *et al.*[5] was used to prepare butenone-2 extracts. Concentrates of urinary factors toxic to mice were obtained through the courtesy of Dr. N. S. Ging.

Chromatographic analysis was carried out in a Chromatocab, using Whatman 1 paper as the stationary phase. The usual solvent systems employed were *n*-butanol; acetic acid: water (12:3:5) and isopropanol: ammonium hydroxide: water (8:1:1) but, in special instances other mixtures were employed as described in the text. Acid chromogens were detected with a spray of sulfuric acid (9N), copper sulfate ($6{\cdot}5 \times 10^{-3}$ M) and glyoxylic acid (1·2 M). Other location and class reagents are described in the body of the paper. Standards were run with each paper.

Glyoxylic acid was obtained either from Calbiochem or freshly prepared from oxalic acid and magnesium to give a 9·2% solution. Chlorpromazine excretion was monitored by the method of EIDUSON and WALLACE[7] and spectrophotometric analysis was carried out using a Beckman DU or a Coleman Universal.

RESULTS

Comparison of sulfuric acid sprays

Various authors have carried out the Reigelhaupt test with glyoxylic acid, acetic acid or water added to a sulfuric acid-copper sulfate mixture. Although all three reagent mixtures appeared to yield very similar qualitative results[2,6] it seemed important to determine whether differences existed in their specificity or reactivity. Consequently, urine concentrates equivalent to 0·5–0·9 ml of whole urine were spotted on Whatman 1, developed with isopropyl: ammonia: water (8:1:1), and separate sheets sprayed with sulfuric acid–copper

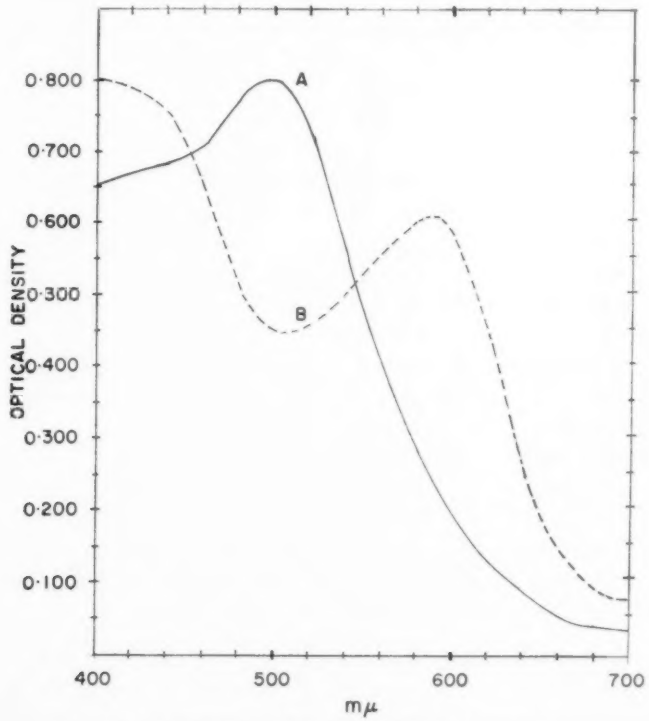

FIG. 1. Absorption spectra of indican chromogens.
Indican absorbed on Whatman 1 was treated with a spray mixture of 9N sulfuric acid and 6×10^{-3} M copper sulfate with (solid line) and without (dotted line) 1·2 M glyoxylic acid. The developed chromogen was eluted with acetone and the spectrum determined with a Coleman Universal.

sulfate mixtures containing glyoxylic acid (1·2 M), glyoxylic acid (1%), acetic acid (8·7 N), or water. Both urine concentrates and untreated whole urine from these subjects gave "positive" glyoxylic acid tests. Indican and 5-hydroxyindole-3-acetic acid were employed as chromatographic markers. All four reagents were found to produce identical patterns of chromogens; however, indican developed a reddish mauve upon treatment with the glyoxylic acid sprays rather than the purple wine observed after the other sprays (Fig. 1).

Despite the apparent equivalence of these mixtures, the glyoxylic acid spray was routinely employed to preclude the possibility of unique reactions.

Specificity and sensitivity of spray reagent

A variety of authentic substances was studied for chromogen production under chromatographic and Reigelhaupt test conditions. The results in Table 1 show good agreement between these procedures despite some differences. Chromogen formation on paper was considerably slower than that in solution and followed a well defined sequence of color development usually proceeding from yellow through pink to some shade of the final hue. Ambient temperature appeared related to the rate of chromogen production and concentration sometimes modified the tint of hues observed. In the series tested, indican was the first to appear (5–15 min) and tryptophan the last (30–60 min).

Differences in the shade of chromogens developed in solution and on paper were not uncommon and, in the case of serotonin, the final hue differed; green to brown-red chromogens developing in solution and pink-green, green-red or purple ones developing on paper. However, in no case was a chromogen detected by the Reigelhaupt test without the corresponding appearance of a distinctive, and usually related, chromogen on paper. The converse was not always true. For example, tryptophan slowly formed a marked red to purple chromogen on paper while only a feeble yellow was seen in the ring test.

The sequential changes in chromogens formed on paper had their parallel color variations in the ring test. Thus, indole variously formed yellow, orange, red, or violet chromogens, psilocybin green to violet ones, and indolacetamide and indoleacetic acid yellow to pink violet ones, apparently depending on the sharpness of the interface and the temperature accompanying sulfuric acid ionization.

Patterns similar to those obtained with the glyoxylic acid spray were observed using 4 N HCl containing copper sulfate (2·6%) or ferric chloride (1%), sodium nitrite in nitric acid, and ferric chloride in perchloric acid, and these mixtures were employed as ancillary sprays.

The glyoxylic acid spray routinely employed could detect less than 2·0 μg of indole-3-acetic, indican, or bufotenine and 5 μg of 5-hydroxyindoleacetic acid. Sensitivity towards other compounds was not determined.

Chromogens in whole urine

Indican. All concentrates contained varying quantities of a substance, identified as indican (Fig. 2), forming a reddish purple upon exposure to glyoxylic acid sprays. This material showed intense, pale blue fluorescence under ultraviolet; an orange-brown color after p-dimethylaminobenzaldehyde and a positive Fluorindal upon exposure to concentrated ammonium hydroxide; a faint orange changing to orange-pink with diazosulfanylic acid: a very light grey with ammonical silver; faint yellow with p-nitroanaline becoming olive after sodium carbonate; an initial pink becoming blue after ferric chloride in HCl; and no reaction with 1-nitroso-2-naphthol. The substance could be removed from neutral urine by passage through a Dow 2 (Cl) or Dow 1 (Cl) column but freely passed Dow 50 (H) and IRC-50 (H). Subsequent elution from Dow 2 could not be achieved. These properties were all identical with those observed for authentic indoxylsulfate run concurrently.

VOL. 1 1962

The Rf of this substance was higher than that of authentic indican when crude urine concentrates were developed with either acidic or basic solvent systems. Band-splitting often could be detected, with urea sandwiched between a top and bottom layer of chromogen, the bottom layer having the Rf of authentic indican. Both layers produced identical chromogens to the full spectrum of location reagents, both were removed from neutral

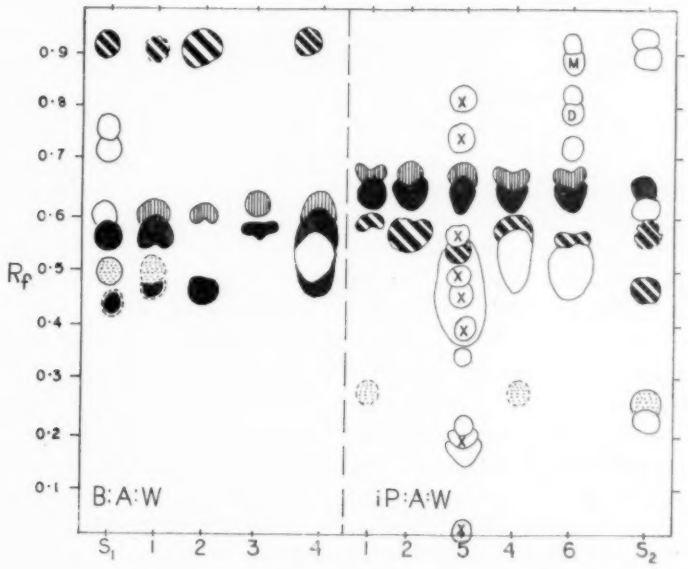

FIG. 2. Composite chromatographic patterns.

Indican designated by black areas, indole-3-acetic acid by lateral stripes, tryptophan by dotted areas and 6-hydroxyskatole sulfate by thin vertical stripes. Dotted outlines designate infrequent occurrence.

S_1 Standards. In order of decreasing Rf, indole-3-acetic, 5-hydroxy-indole-3-acetic, tryptamine, bufotenine, indican, tryptophan. Dotted blackened area shows position of indican in the absence of urea.

1. Urine concentrate developed with glyoxylic acid spray.
2. Butanol extract of urine developed with glyoxylic acid spray.
3. Urinary "toxic" factor extract developed with glyoxylic acid spray.
4. Urine concentrate developed with Ehrlichs' reagent.
5. Urine concentrate of subject on chlorpromazine developed with glyoxylic acid spray. Areas marked "X" were removed by passage through Amberlite IRC-50.
6. Butenone extract developed with Ehrlichs' reagent. "M" designates "Mauve Factor", "D" designates "Depression Factor".

S_2 Standards. In order of decreasing Rf, bufotenine, tryptamine, indican, serotonin, indole-3-acetic acid (in presence of urea), indole-3-acetic acid, tryptophan and 5-hydroxyindole-3-acetic acid.

Developed chromatograms were copied and reduced in size by use of a pentograph and Rf's were corrected on the basis of concurrently run standards.

solution by Dow 2 (C1) and Dow 1 (C1), and the Fluorindal reaction showed permeation, through urea, between the bands. Permeation could be enhanced by addition of authentic indican to the sample, and both Rf elevation and band splitting could be replicated by addition of urea to authentic indican. Urease pretreatment of urine concentrates decreased

the Rf so that it was equal to (basic solvent systems) or only slightly greater than (acidic systems) that obtained with synthetic indican and eliminated band splitting. Both indican and the urinary substance had identical Rf's in the neutral solvent systems *n*-butanol: ethanol: water (4:1:1), and 75% ethanol in water. Two-dimensional chromatography of a urine concentrate-indican mixture with isopropanol: ammonia: water (40:1:9), and *n*-butanol: acetic acid: water (4:1:1) revealed only one spot with the characteristic red-wine of indican.

Because of its universal appearance, no diagnostic significance could be attached to the qualitative presence of this material. Further, there appeared to be no relationship between diagnosis and a crude quantitative index, based upon a one-to-five rating of chromogen intensity divided by the urinary equivalent applied.

6-Hydroxyskatole Sulfate. Glyoxylic acid treatment of chromatograms often elicited a stable blue chromogen with a characteristic position just above indican in both acidic and basic solvents. Darkened trails of fast running compounds sometimes obscured its presence in the former case. This material corresponded in Rf to a bright blue-green fluorescent area most clearly seen after development with isopropanol: ammonia: water mixtures. The fluorescent characteristics of this substance are shown in Fig. 3.

Treatment with Ehrlichs' dip resulted in the appearance of a bright cobalt blue which faded at a variable rate, sometimes completely disappearing in less than a minute, on other occasions changing to a relatively persistent greyish-blue-green. This variance was a characteristic of the run and did not reflect differences in the samples under examination. Exposure to ammonium hydroxide in the Fluorindal reaction led to the immediate disappearance of color without eliciting discernible fluorescence. Diazotized sulfanilic acid — ammonium sulphamate elicited the violet chromogen presumed characteristic of 6-hydroxyindoles. The material could be removed from neutral solutions by passage through Dow 1 (Cl) but not Dow 50 (H) and could be partly extracted into butanol and methyl ethyl ketone.

Although authentic material was not available for comparison, the chromatographic characteristics, color reactions, and ionic properties of this substance are in conformity with those reported for 6-hydroxyskatole sulfate.[5,8] Failure to elicit the orange-red Fluorindal fluorescence, reportedly[9] characteristic of skatole indicanoids, may be due to interfering substances in the samples or, more likely, may indicate that 6-hydroxyskatole sulfate is an exception to this reaction since others[3,13] have also obtained negative reactions with their corresponding materials.

This substance also appears to be identical to that material variously called "Q. F. B.",[3,10] "Spot 2",[11] "5",[12] "U–2",[13] and "Q",[14] reported more frequently in urine from schizophrenics than from normals. In this study, Ehrlichs' reagent indicated the presence of this substance in 65 per cent of the urines from schizophrenics, it appeared to be absent in 30 per cent and was equivocal in 5 per cent. On the other hand, 63 per cent of the urines from non-schizophrenics showed this material, it was absent in 27 per cent and equivocal in 10 per cent. If the blue chromogen produced with glyoxylic acid was taken as a criterion, 46 per cent of the schizophrenics showed this substance as against 43 per cent of the non-schizophrenics. A blue glyoxylic acid chromogen always had a corresponding cobalt blue Ehrlichs' reactor. The converse was not always true, presumably because of the

VOL. 1 1962/

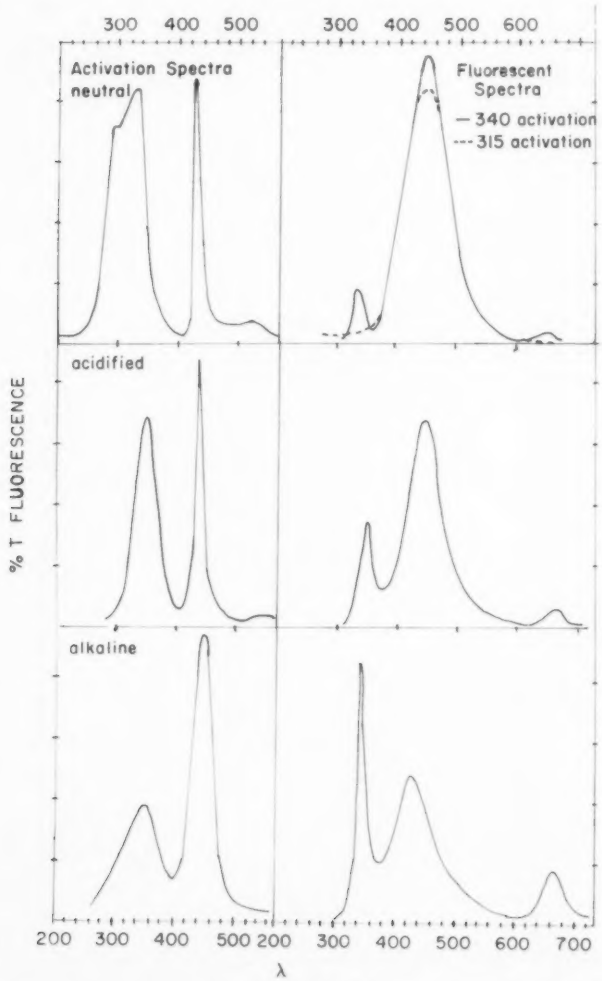

FIG. 3. Fluorescent characteristics of 6-hydroxyskatole sulfate (?)
Material thought to be 6-hydroxyskatole sulfate was located on chromatograms by characteristic placement relative to indican, blue green fluorescence, and position, of material forming a quickly-fading cobalt blue after Ehrlichs' reagent and a blue grey after glyoxylic acid reagent. Corresponding regions of the untreated chromatogram were excised, homogenized in water and passed through a Millipore filter. Fluorescent characteristics of the solution were determined in neutral, acidic (2 N HCl), and basic (2 N NaOH) solution using an Aminco Bowman Spectrofluorophotometer.

greater sensitivity of the Ehrlichs' reagent. The Reigelhaupt test on a butanol concentrate of this material eluted from chromatograms elicited a pale brown, violet, to red ring and a lavender solution after mixing (Table 1).

The incidence of this substance in urines from schizophrenics agrees with other findings. The high incidence among controls, however, differs from some reports, especially those

TABLE 1. COMPARISON OF ACID CHROMOGENS UNDER REIGELHAUPT AND CHROMATOGRAPHIC CONDITIONS

Compound***	Reigelhaupt Test*		Chromatographic**	
	Ring	Solution	0–2 hr	24–48 hr
Indoles				
Bufotenine Oxalate‡	G-GB	G	R-G	GBk
Dimethyl tryptamine§	P	R-Bn	G	G
5-Hydroxytryptophan‡	G	G	G	G
5-Hydroxytryptamine creatinine sulfate‡	RBn-G	G	R-G	GyG-P
5-Hydroxyindoleacetic acid cyclohexylamine‡	YG-P	G-GyP	Pi-G	GyG
6-Hydroxyskatole sulfate?††	Y-B-R	Pi-R	B	BGy
Indole†	Y-O-R-V	pY-R	O	R
Indole-3-carboxylic acid‡‡	fY	fY	X	—
Indole-3-acetic acid†	Y-PiV	YPi-V	Y-Pi	GyG-Pi
Indole-3-propionic acid†	GY	Y	X	—
Indole-3-butyric acid†	Y	Y	X	—
Indole-3-acetamide¶	Y-PiV	Y-V	Y-Pi	Pi-G
Indoxyl-o-sulfate‡	V-PR	V	Pi-RV	RV
Psilocybin§	G-V	G	GyG	GyG
Skatol	Y-R	YO-OR	Y-R	P-PR
Tryptamine . HCl†	YBn	RBn	Y-Pi	GyG
Tryptophan†	Y	X-Y	fPi	PB
Catecholes				
3,4-Dihydroxy phenylalanine‡	X-Gr	Gr	Pi(s)	Bn(s)
Epinephrine . HCl‡	Y	Y	fPi(s)	Bn(s)
Norepinephrine . HCl‡	Y	Y	fPi(s)	Bn(s)
Phenothiazines				
Chlorpromazine . HCl‖	RV	RV	RV	RV
Imipramine§§	YG	fG	X	Y
Prochlorperazine‖	RV	RV	RV	RV
Trifluoperazine‖	RV	RV	RV	RV
Miscellaneous				
Creatinine†	X	X	X	X
Histamine†	X	X	X	X
Kynurenine†	X	X	X	X
Kynurenic acid†	X	X	X	X
Proline†	X-fY	X	X	X
Thorzylamine . HCl	RV	RV-P	Pi	Pi
Urea†	X	X	X	fYBn
Uric acid†	X	X	X	X

* The reaction solution consisted of the compound in 3·2 ml of 1·2 M glyoxylic acid and $6{\cdot}5 \times 10^{-3}$ M copper sulfate to which was added 0·2 ml of *n*-butanol. The chilled solution was slowly underlayed with 2 ml of 36 NH_2SO_4 and the color of sharp and stirred interface noted (column 1). The two phases were slowly mixed by swirling in an ice bath and the color of the solution estimated after 10 min (column 2).

** Compounds were chromatogrammed in isopropanol : ammonium hydroxide : water (8:1:1) and chromogens developed with a spray consisting of sulfuric acid (9N), copper sulfate ($6{\cdot}5 \times 10^{-3}$ M) and glyoxylic acid (1·2 M). Some compounds such as tryptamine . HCl_2 formed "iso-smears" under these conditions and the colors reported are those for both major and minor spots.

*** †Nutritional Biochemicals; ‡Calbiochem; §Sandoz Pharmaceuticals; ‖Smith Kline and French; ¶Mann Biochemical; ††eluted from undeveloped chromatograms (see text); ‡‡courtesy Dr. F. Campbell, Parke Davis & Co.; §§Geigy.

Symbols: X = no color; B = blue; Bn = brown; Bk = black; G = green; Gy = grey; O = orange; P = purple; Pi = pink; R = red; V = violet; Y = yellow; f = faint; (s) = streaks; — color range.

VOL. 1 1962/

using hospital personnel or normal volunteers as the comparison population. It does agree with other findings, of high incidence among all mentally ill subjects[11] and among "organic psychosis," "complicated affective disorders," and "complicated neurosis".[10]

Indole-3-acetic acid. Two pinkish spots also were seen occasionally in whole urine. The first was tentatively identified as indole-3-acetic acid on the basis of: co-chromatography with authentic indole-3-acetic acid; oxidation by nitrite-nitric acid to a bright pink slowly going to brown; reaction with ferric chloride-perchloric acid to a bright pink; and formation of a pink to purple color eventually turning blue with Ehrlichs' reagent. Its Rf in untreated urine concentrates exceeded that of authentic material in basic solvent systems, where it appeared just above urea. Addition of urea to authentic compound resulted in a similar elevation in Rf and pretreatment with urease decreased it to that reported in the literature. The Rf in acidic solvents corresponded with literature values but its detection with the glyoxylic acid spray was often difficult because of the darkened trails of fast moving compounds. Its presence could be demonstrated with Ehrlichs' or with oxidizing reagents. Glyoxylic acid spray revealed this material in about 10 per cent of both schizophrenic and non-schizophrenic subjects and its presence was apparently unrelated to clinical state. Ehrlichs' reagent elicited it in 80 per cent of the urines from subjects in both diagnostic categories.

Tryptophan. The fourth chromogen, was observed particularly in a limited series of "Reigelhaupt positive" urines in which precipitate from the urinary concentrate was employed. The material was present in urines from 4 of 13 schizophrenics and 1 of 3 non-schizophrenics. It gave the same color reactions as tryptophan and had the same Rf in the solvent systems *n*-butanol: ethanol: water (4:1:1) and *n*-butanol: acetic acid: water (4:1:5). Further attempts at identification were not made both because it appeared unrelated to diagnosis and because of its infrequent occurrence even in "positive" urines.

n-Butanol Extracts. Chromatograms of butanol extracts equivalent to 6–8 ml of whole, positive-reacting, urine revealed only three chromogenic spots. Two of these were common to all urines and were identified as indole-3-acetic acid and indoxyl sulfate on the basis previously described. The third substance appeared in one of the four urines and had the properties already described for 6-hydroxyskatole sulfate. Interestingly the indole-3-acetic acid spot was considerably more intense in these extracts than in whole urine, while indican showed the reverse trend.

Urinary toxic factors. Five biologically potent extracts[4] were chromatographically examined individually and in an equal volume pool, and were compared to a pool of biologically weak extracts. All of these crude extracts gave a weakly positive Reigelhaupt test and contained a single glyoxylic acid chromogen, indican; one also contained 6-hydroxyskatole sulfate. Chromogens could not be observed with purified preparations of the biologically active components, and such preparations produced only a faint brown ring on the Reigelhaupt test. Whatever their nature, these substances are clearly unrelated to the active principal in the Reigelhaupt test.

Butenone-2-Extracts. Three glyoxylic acid chromogens were detected in volumes of butenone-2-extracts of ether-extracted urine equated to 2·5 mg of creatinine. Indican was observed in all cases and no relation was found between intensity of color and any pathological index. Indole-3-acetic acid was observed in 38 per cent of the extracts from

schizophrenics and 31 per cent of those from non-schizophrenics. The third substance, identified as 6-hydroxyskatole sulfate, was observed in urines from 46 per cent of the schizophrenics and 57 per cent of the non-schizophrenics. Somewhat higher figures were obtained with Ehrlichs' dip reagent, where "Quickly Fading Blue" was present in 63 per cent of the schizophrenics, absent in 26 per cent, and ambiguous in 11 per cent, as against 76 per cent positive, 12 per cent negative, and 12 per cent uncertain among non-schizophrenics.

Several other Ehrlich-reactors were observed on chromatograms developed in isopropanol-ammonia-water. Among these were substances apparently identical with the recently described "Mauve" (associated with psychosis) and "Depression" factors.[15] The "Mauve Factor" had an Rf of 0·89–0·92 (Bufotenine control = 0·92) forming a red-purple product after Ehrlichs' reagent, which slowly turned dusky lavender. This substance was found in 66 per cent of the schizophrenic and 38 per cent of the non-schizophrenic populations — the greatest difference encountered. Three of the 7 most psychotic subjects in this study (determined by psychological testing) were negative, however, as was the only non-schizophrenic considered possibly psychotic. The 3 non-schizophrenics excreting this material showed no evidence of psychotic derangement. Only a 43 per cent concordance was observed between this factor and quickly-fading-blue material although both are purportedly related to psychosis. The Depressive Factor had an Rf of 0·77–0·80 and formed a pink-red product with Ehrlichs' reagent. This substance was detected in 66 per cent of the schizophrenics and 71 per cent of the non-schizophrenics. Of the three subjects considered as greatly depressed, two excreted this material and one did not.

Medication. Many phenothiazines react with strong acid to produce chromogens and a number of analytical tests for this compound are based upon this reaction (Table 1). Urines of subjects treated with chlorpromazine often produce purple-lavender chromogens in the Reigelhaupt test. Therefore, it seemed important to examine urines of phenothiazine treated subjects for glyoxylic acid chromogens to assess the extent of phenothiazine interference with the Reigelhaupt test.

The urines of 5 schizophrenic subjects (receiving 150 mg of Thorazine Concentrate daily for three weeks) were concentrated and chromatogrammed. Between 6 and 13 glyoxylic acid chromogens were observed, 4 to 11 of which were never observed in urines of untreated subjects. These chromogens ranged in color from grey-green to red-pink. Among all the chromogens observed, 3 to 6 (including indican and 6-hydroxyskatole sulfate) were not adsorbed by Amberlite IRC-50. The nature of the remaining chromogens has not been investigated but these results clearly indicate both that phenothiazine metabolites cannot be ignored in studies involving chromogen production and that assays for phenothiazine metabolites which are dependent upon Amberlite IRC-50 adsorption may not account for all its metabolic products.

DISCUSSION

In an earlier study on the Reigelhaupt test, a high and equal incidence of "positives" was found among both schizophrenics and non-schizophrenics. These results could have been due to an overgenerous criterion of a positive reaction or to the experimental introduction of an extraneous masking chromogen. The first explanation could account for the high incidence of positive tests but would indicate also that the procedure had little

VOL.
1
1962/

diagnostic relevance, inasmuch as the criteria were the same for both groups. The results of the present study strongly mitigate against the second explanation as well.

A glyoxylic acid chromogen unique to schizophrenics might avoid detection by failing to form chromogens on paper while forming them in solution. No example of such behavior was observed upon testing a variety of diverse compounds. A unique chromogen might escape detection if it were unstable to the acidic, neutral and alkaline chromatographic solvents employed. Such instability is possible but unlikely. Finally, the compound could have been destroyed or lost in sample preparation. Because of the variety of preparations employed, however, this could only occur if the substance were both strongly polar in acidic solution and yet distilled from it during reduced pressure evaporation, and were either not adsorbed onto charcoal or not eluted from it by alkaline acetone water. Few compounds could fit these criteria.

OL.
1
62/63

The results also demonstrate the lack of specificity of this test. Three of the chromogens detected in these studies produce a positive Reigelhaupt test and at least two of them, indican and indole-3-acetic acid, are common in normal urine. A wide variety of other compounds, including some of the most common therapeutic agents in psychiatric medicine, also produce red to violet chromogens and more positive Reigelhaupt tests than otherwise observed in this laboratory. The observation that chlorpromazine elevates indican excretion and that elevated urinary chlorpromazine and indican levels may persist for significant periods after termination of chronic medication[2] makes it possible that the reported difference between diagnostic populations is due to treatment, not disease. Other workers have reached similar conclusions.[16,17]

The requisite metabolic pathways for 6-hydroxyindole formation have been demonstrated in mammalian tissues[18,19] but their relationship to endogenous psychosis is uncertain. Six-hydroxyskatole sulfate itself is probably formed exclusively by intestinal flora[8] and its equal incidence among schizophrenics and non-schizophrenics in this study strongly suggests that factors other than disease account for its apparent relationship to schizophrenia. The comparison population in this study consisted largely of non-schizophrenic sociopaths differing from hospital personnel and other "normal" controls not only in psychopathology but probably more critically, in sharing with schizophrenics the identical environment, diet, activity restrictions and the like, and so presumably their intestinal flora and any endogenous subclinical infections. The similar findings in our populations may well reflect this greater control for similarity in environment.

Parallel comments apply to the present observations on the "Mauve" and "Depression" factors. Although the preparations employed differed from those of the original worker,[15] their lack of diagnostic relevance in this study again suggests that spurious factors account for earlier findings of differences. In no case was bufotenine detected in urinary preparations although the location reagents employed were sensitive to this compound. Again these preparations differed somewhat from those employed in the original reports,[20] but this could hardly be decisive. Interestingly enough, bufotenine has a simlar Rf to 6-hydroxy-skatole sulfate in butanol: acetic: water (12:3:5) and could conceivably have been mistaken for it.

SUMMARY

A chromatographic analysis failed to detect any glyoxylic acid chromogen unique to schizophrenics in whole urine, butanol extract, butenone-2-extracts, or charcoal purified preparations. Compounds identified as indican, indole-3-acetic acid, 6-hydroxyskatole sulfate, and tryptophan were detected in the preparations examined. The incidence and intensity of these materials was identical for both schizophrenic and non-schizophrenic populations. The results support the view that the Reigelhaupt test has little diagnostic significance.

The incidence of the compounds designated "Quickly Fading Blue", and "Depression Factor" in preparations from both schizophrenic and comparably handled non-schizophrenic hospital populations was the same as that generally reported for schizophrenics. "Mauve Factor" had a higher incidence among the schizophrenics but none of these substances appeared specifically related to pathology.

No evidence for the occurrence of bufotenine could be found in urinary preparations from either schizophrenics or non-schizophrenics.

The results are discussed in relation to true and spurious factors, and the importance of control of many environmental factors is stressed.

VOL.
1
1962

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OL.
1
62/63

VOL.
1
1962/

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AUDITORY AND VISUAL INTERACTION IN IMMEDIATE MEMORY*

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OL.
1
62/63

1. INTRODUCTION

MUCH of our understanding of immediate or short-term memory has come from studies based on a general method of presenting information to subjects (*S*s) who are then asked to recall, reproduce or recognize as much of that material as they can. The digit span experiment is a well known example of this type of approach.[1] MILLER[2] has indicated that the immediate memory span is about seven items and appears to be limited by number of items rather than amount of "information." In recent years some new methods have been developed to extend the study of immediate memory beyond the limitations of the classical methods. AVERBACH and SPERLING'S[3,4] use of sampling techniques which require recall of only (randomly selected) portions of material presented indicates that considerably more items are available to a *S* than the four or five he can report after tachistoscopic exposure of many more. Other methods have been developed to study short-term memory-in-process, so that the availability of information in a storage to which more new items have been added may be estimated.[5–12] SHEPARD and TEGHTSOONIAN[13] recently demonstrated that correct recognition of repetitions of numbers is inversely proportional to the number of intervening items between first presentation and repetition. These developments lead to the following general method for investigation of immediate memory-in-process.

If a series of random displays (for example, random numbers) is presented sequentially to a *S*, who is instructed to indicate only that he notes the repetition of any display (number) previously presented, then correct identification of random repetitions will provide an estimate of the amount registered for short-term retention. It may be inferred that under these circumstances preceding displays were retained, each new display being compared with those still retained in order to correctly identify a repetition. Thus this is a sampling procedure which utilizes the repetition of any display as the indicator for the *S*'s responses. Since the signal acts as its own indicator for the type of response required it is not necessary to introduce extraneous, possibly distracting, auditory or visual indicators. Because such a sampling technique demands a minimal subject response to estimate the amount (and character) of information registered and retained it provides a greater estimate of immediate memory storage than can be obtained by the use of classical recall or reproduction techniques. Together with classical recall or reproduction methods, this provides independent estimates of information registered in and information retrieved from the im-

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mediate memory storage, permitting differential study of factors affecting registration and retrieval.[14] A further advantage is the great degree of control offered to the experimenter which is especially useful for the study of immediate memory in brain injured *S*s whose repertoire of responses may be limited.

It is possible that this method may offer both an operational definition and a method for the study of "scanning" within the central nervous system, inasmuch as information retained in the nervous system must be "scanned" (in a sense implied by this experimental procedure) for each new display to determine if it is a repetition. The present study offers an illustration of how the character of information may affect such "scanning." To study auditory and visual interaction[15,16] in immediate memory[17–22] this method was modified in the following manner. The *S* was presented with short sequences of displays, each of which consisted of the simultaneous visual and auditory presentation of two different, randomly selected numbers, and was instructed to indicate only his recognition of the repetition of any number presented earlier in the same short sequence. That is, the *S* heard a short series of randomly selected numbers, one every 2 sec and each time he heard a number he simultaneously saw another number. He was instructed to push a button whenever he either saw *or* heard a number that he had already either seen *or* heard before. In other words, the *S* had to pay attention to two different but simultaneously presented sequences of serially presented numbers, one auditory and the other visual so that he might identify any repetitions. By arranging series and repetitions so that numbers were presented and repeated randomly but equally in both modalities and so that numbers presented in both channels were repeated equally often in either modality it became possible to inquire whether immediate memory might be modality specific; i.e. to what extent can *S*s correctly recognize visual repetitions of aurally presented information and auditory repetitions of visual information?

VOL.
1
1962/

2. METHOD

Subjects

This experiment is based on data from 36 *S*s, 8 of whom may be considered as experienced because they had participated in a similar experiment at least once previously, while the remaining 28 *S*s were naive. Since there were no significant differences ($p > 0{\cdot}05$ by the t-test) between the behaviour of naive and experienced *S*s the data from both groups were pooled. The group of 36 *S*s consisted of 11 females and 25 males, ranging in age from 18 to 38 years; all but 3 were between 20 and 32 years with a mean age of 25·4 years. The *S*s were medical students, technicians and secretaries at the Albert Einstein College of Medicine and were paid for their participation.

Procedure

The *S*s were tested individually while seated in a 3 ft. × 4 ft. × 6 ft. sound dampened booth. Before each test session the *S* was told only that this was an experiment involving memory. Subjects were told that in scoring, hits and correct rejections would count for them while false alarms or misses would count against them. All *S*s took a control test first. Each test session lasted 20–25 min, with about 3 min rest between control and experimental test. Before each test they were given a card with the following instructions which were then discussed with each *S* until he understood them clearly.

Instructions for the control test: "You will be shown some numbers on the panel in front of you. Each time you see a number you will also simultaneously hear a number. The numbers will be presented in several short series. You should press the key on the shelf whenever the numbers that you see and hear are the same. The numbers that you will see and hear run from 1 through 7 and from 10 through 17; numbers 8 and 9 will never be used. Press the key only if the numbers you see and hear are exactly the same."

Instructions for the experimental test: "You will again see and hear the same numbers presently simultaneously in short series. This time you should press the key only when any of the numbers that you see *or* hear is a repetition of some number that you have already seen *or* heard within the same short series. The first numbers that are presented in each series are obviously not repetitions, but any of the following numbers seen and heard in the same series may be a repetition of some number already either seen or heard in that series."

Visual presentation of numbers was by means of two Burroughs Corp. standard "NIXIE" tubes (which show characters 6–10 in. high readable at 35 ft) mounted 1 in. apart at eye level, 2 ft in front of the *S*. The visual presentations were programmed by a teletype tape unit. The right-hand tube showed numbers 1–7, while for higher numbers (10–17) both tubes were used. Auditory presentation was by means of recorded tapes played on a Wollensak Model T–1500 tape recorder. For purposes of coordinating auditory and visual presentation both tests were preceded by two sample sequences of the numbers in serial order. The *S* indicated the appropriate response by pressing the button of a microswitch whenever a repetition was seen or heard. Responses were recorded on tapes by a teletype system.

Experimental design

Each *S* was presented with 32 short groups of simultaneous visual and auditory displays, each group separated from the preceding and following group by a silent interval of 10 sec. Each short group consisted of a sequence of 9 consecutive visual presentations of some number together with simultaneous presentation of another number aurally. One simultaneous auditory and visual display was presented every 2 sec. Both the aural and the visual number were presented for approximately $\frac{1}{2}$ sec, followed by a silent interval of $1\frac{1}{2}$ sec before the next presentation; the *S* was allowed the full 2 sec from the onset of one display until the onset of the next in which to indicate his response. An illustration of such a short group is shown in Fig. 1.

A (auditory)	7	12	1	5	1	4	11	16	2
B (visual)	17	5	10	13	15	3	15	6	11
				R	R		R		R
	1	2	3	4	5	6	7	8	9
	Display								

FIG. 1. Sample group of sequential displays from experimental test with simultaneous presentation of numbers in auditory and visual modalities. *R* indicates that display contains a repetition of an earlier presentation.

The experimental protocol was designed so that 50 per cent correct could be obtained by chance alone. Four of the last 8 displays of each group of 9 included a visual or aural repetition of some number which had been presented visually or aurally once before *within* that *same* series. The entire battery of 32 groups was so arranged that 16 of those 32 simultaneous auditory-visual displays which were second (through ninth) in the short groups included a repetition of some number previously seen or heard. Excluding the set of first displays 128 of 256 simultaneous auditory-visual displays calling for response included a repetition of some number presented earlier in its own group. In any simultaneous auditory-visual display only one of two numbers presented was a repetition. All repetitions occurred after only one intervening display, except those occurring in the second displays, which were repetitions of numbers presented in the first display of any group; *S*s were neither subjectively nor objectively aware of this design (see Fig. 3). The 15 numbers used in this experiment were numbers 1 through 7 and 10 through 17 and all numbers were used randomly but equally throughout the test.

In the design of the 32 groups, 4 variations of 8 basic groups were constructed randomly so that the same repetition in any display would be a repetition of the same number: once as an auditory repetition of an earlier auditory presentation (*AA*), once as an auditory repetition of an earlier visual presentation (*BA*), once as a visual repetition of an earlier visual presentation (*BB*), and once as a visual repetition of an earlier auditory presentation (*AB*). In the notation used here *A*- indicates information initially presented aurally and *B*- information initially presented visually, while -*A* refers to repetition in the auditory modality and -*B* refers to repetition in the visual modality. The 32 groups thus designed were then arranged in a random order for presentation. To balance effects of learning and proactive interference, half of the *S*s were given the test in this random forward order, while the other half were given the reverse order.

A control test without repetitions was similarly designed also using simultaneous aural and visual presentation of numbers, but *S*s were instructed to press the button whenever the numbers simultaneously seen *and* heard were identical. The display parameters of this control were the same as in the experimental test except that only the eight basic groups were used. Figure 2 shows a sample group from the control test.

Control test

A (auditory)	5	10	6	12	15	3	11	16	17
B (visual)	14	10	6	7	15	1	13	4	17
		*	*		*				*
	1	2	3	4	5	6	7	8	9
	Display								

FIG. 2. Sample group of sequential displays from control test with simultaneous presentation of numbers in auditory and visual modalities. Asterisk indicates that display contains presentations of the same number in both auditory and visual modalities.

VOL. 1 1962

3. RESULTS

(a) *Control test*

Overall 99·2 per cent of pushes were correct, 98·0 per cent of non-pushes were correct and the overall average was 98·6 per cent of all responses correct. Fifteen *S*s performed without any errors, 15 with only 1 error, 4 with 2 errors, and 2 *S*s with 3 and 4 errors respectively.

(b) *Experimental test*

General performance. No significant changes or trends in performance were apparent through the course of the test (i.e. from group 1 through group 32) for either the entire group of *S*s or those 18 *S*s who took the forward order of the test.

OL.
1
62/63

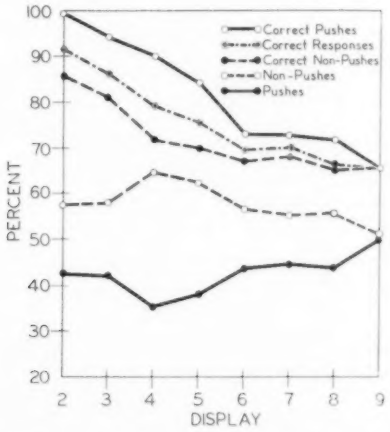

FIG. 3. Response bias in experimental test.

Figure 3, describing the results by displays, shows the percentage of responses that were pushes and the percentage of those pushes that were in fact correct identifications of repetitions.

Analysis of auditory-visual interaction. (i) The contribution of auditory and visual inputs to information retained by immediate memory storage is shown in Fig. 4. This indicates that the gradual decline in information retained (shown as percentage of correct pushes in Fig. 3) derives principally from the more severe decline of correct recognition of visually presented information (*B*-). This is reflected in an overall average retention of 76·2 per cent of the auditory information presented in contrast to an overall average retention of 59·5 per cent of the visual information presented. The difference between *A*- and *B*-, which is significant by the t-test ($p<0{\cdot}01$), is shown in another form in Fig. 6. While, as Fig. 4 shows, recognition of both *A*- and *B*- decreases after presentation of a total of 4 numbers (display 3), the greatest decrease in retention is found when 2 more numbers (for a total of 6) are presented (display 4). As more auditory-visual presentations are added, recognition of

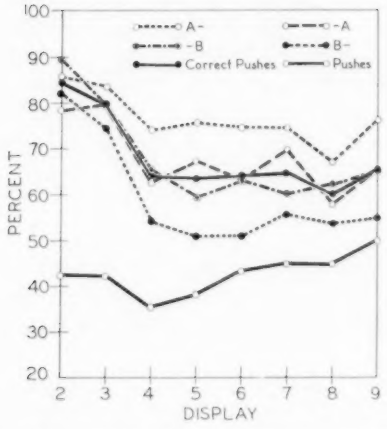

FIG. 4. Correct recognition of repetition of information presented. Auditory presentation is indicated by *A*-, visual presentation by *B*-. Auditory repetition is indicated by -*A*, visual repetition by -*B*.

both *A*- and *B*- remain relatively constant (displays 5 through 9), suggesting that something approaching a steady state may be reached.

(ii) Figure 4 also indicates a second finding, namely that both visual and auditory presentations are equally effective as probes for retrieving material from immediate memory storage. Figure 5 shows that auditory and visual presentations each retrieved 50 per cent

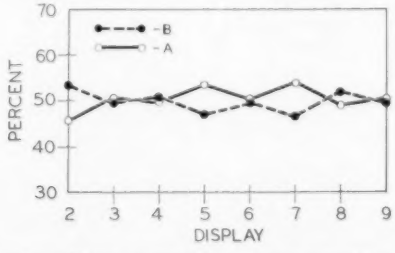

FIG. 5. Per cent of correct recognitions of repetitions when repetition was auditory (-*A*) and when repetition was visual (-*B*).

of the total information retrieved. There is no significant difference between -*A* and -*B* ($p > 0{\cdot}05$ by the t-test).

(iii) A third finding is shown in Fig. 6 which demonstrates that both auditory and visual probe presentations retrieve both auditory and visual information from immediate memory storage in the proportion that auditory and visual information contribute to the total available information. That is,

$$\frac{AA}{AA + BA} = \frac{A\text{-}}{(A\text{-}) + (B\text{-})} = \frac{AB}{AB + BB} \text{ and } \frac{BA}{AA + BA} = \frac{B\text{-}}{(A\text{-}) + (B\text{-})} = \frac{BB}{AB + BB}$$

This finding is *not* entailed by the two previous findings; it is quite conceivable, for instance, that, while *A*->*B*- and -*A* = -*B*, auditory probes might have retrieved more auditory than

visual input and visual probes might have retrieved more visual than auditory input.

There is no significant difference between recognition of auditory repetitions of auditory information (*AA*) and visual repetitions of auditory information (*AB*); $p>0{\cdot}05$ by the t-test. The slight difference between the per cent of visual information retrieved by visual probe

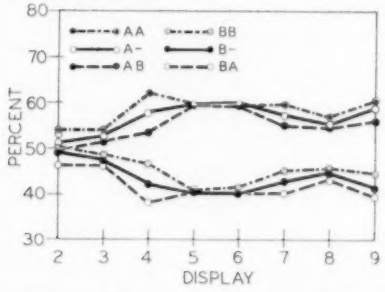

FIG. 6. Per cent of correct recognitions of repetitions by type of input, where auditory input is given by *A*- and visual by *B*-. Note that correct recognition is a function of retention of visual or auditory input so that *AA* and *AB* are correlated with *A*- while *BB* and *BA* are correlated with *B*-. (*AA* = visual repetition of auditory presentation; *AB* = visual repetition of auditory presentation; *BB* = visual repetition of visual presentation; *BA* = auditory repetition of visual presentation.)

repetition (*BB* = 52 per cent) and visual information retrieved by auditory probe repetition (*BA* = 48 per cent) is significant by the t-test ($p<0{\cdot}01$). However, although visual probes retrieved 4 per cent more of the total visual information retrieved than did auditory probes, the retrieval of visual information by visual probes (*BB*) and by auditory probes (*BA*) shows a high degree of correlation ($r = 0{\cdot}93$). Furthermore, neither is well correlated with the

Results

A = auditory	B = visual
A- > B-	Input retained
-A = -B	Effectiveness of probe repetitions
$\frac{AA}{BA} \gtrless \frac{A-}{B-} \gtrless \frac{AB}{BB}$	Relation of probe and input modalities
$\frac{AA \gtrless AB}{BB \gtrless BA}$	

FIG. 7. Summary of results.

retrieval of auditory information: the correlation between *BB* and *A*- is given by $r=0{\cdot}10$, and that between *BA* and *A*- is given by $r=-0{\cdot}17$ (these correlation coefficients are significant by the t-test [$p<0{\cdot}01$]).

These data for the group of *S*s as a whole are also characteristic of the individual behavior of 86 per cent of the *S*s. *A*- > *B*- for 33 *S*s and *A*- = *B*- for the other three. -*A* = -*B* for 3 *S*s, while -*B* > -*A* for 13 others and -*A* > -*B* for the remaining 20, although these differences were *not* significant ($p>0{\cdot}05$).

4. DISCUSSION

THE results of the control test would indicate that (a) there were no *S*s with auditory or visual impairment, (b) visual and auditory presentations were readily perceived as presented (i.e. were suprathreshold), and (c) there is almost no difficulty at all in perceiving, transforming and comparing information and responding correctly at the rate of one simultaneous auditory and visual presentation every 2 sec. This method should be useful for further study of shifting of attention between channels.[17]

The principal data to be interpreted are the three findings noted above: (a) More auditory than visual input was retained (*A- B-*). (b) Auditory and visual inputs were equally effective as probes for retrieving information (*-A -B*). (c) Both auditory and visual probes retrieved information from immediate memory storage in proportion to the contribution that previous auditory and visual input made to the total retrieved information (*AA/BA: A-/B-: AB/BB*).

Under the conditions of this experiment the possibility of rehearsal by *S*s during the interval between presentations cannot be excluded. Such rehearsal might allow *S*s to translate visual information into auditory for storage. Until these possibilities have been experimentally evaluated, interpretation of the present data is limited. Should these possibilities be excluded or their effects controlled by further studies, the following considerations might suggest a tentative interpretation of the present data.

If auditory and visual input was stored separately it might be expected that (i) repetitions in the same modality would have been recognized more frequently than repetitions in the other modality, and thus that (ii) auditory repetitions would have been recognized more frequently than visual repetitions, unless both modes of input had effectively equal access to both storage systems. This latter possibility remains to be studied experimentally.

If both modes of input were stored in some common auditory or visual storage, it would more probably have been a common auditory storage since more auditory input was retrieved. It might then be expected that (i) auditory probes would have retrieved more information than visual probes, and that (ii) auditory probes would have retrieved more auditory input than visual probes.

As these expectations are not supported by the present data, the possibility should be considered that both modes of input might have been stored in some common storage system that was neither auditory nor visual. If this were the case, there would appear to have been a differential "decay" of auditory and visual input during storage, since the equal efficacy of both modes of presentation as retrieving probes would indicate that both were equally well attended to, perceived, and transformed when storage was not involved. The differences between these two modalities which might give rise to such a differential "decay" cannot be deduced from this experiment in which suprathreshold stimuli were used but may emerge from further studies in which parameters of the stimuli relevant to attention, perception, and transformation are explored.

VOL.
1
1962/

5. SUMMARY

Simultaneous auditory and visual displays of different numbers were presented serially to 36 normal human subjects who were instructed to indicate their recognition of any repetitions in each series so that homo-modal and hetero-modal retrieval from immediate memory storage might be compared. Auditory input was retained best, repetitions in either modality were equally effective in retrieval, and retrieval of both modalities of input was proportional to their contribution to total retained input.

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OL.
1
62/63

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VOL.
1
1962/

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DIMENSIONS OF MANIFEST DEPRESSION

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OL.
1
62/63

DEPRESSION is a complex psychiatric concept. The term is used to refer to subjective mood as well as to symptom syndromes associated with psychopathologic states called depression. As a psychiatric syndrome, depression is manifest in a number of signs and symptoms which distinguish the depressed patient from the normal. As in the case of other recognized syndromes, not all depressed patients evidence all symptoms, at least not to the same degree of intensity. An important question concerns characteristics of individual difference in depressed patients. If depressed patients vary in the nature and intensity of symptoms presented, what primary symptom dimensions are most useful in characterizing these individual differences? Must variation in the symptomatology of depressed patients be accounted for in terms of a unique set of factors which are not recognized dimensions of psychiatric symptomatology in other patient populations, or is there a common set of factors which exist at different levels in various types of psychiatric patients including cases of depression?

The methods of factor analysis were employed in the present investigation in an effort to provide answers to these questions. The factor analysis model assumes that observed behavior is complex and that it is determined by a parsimonious set of underlying factors, traits, or processes. Any given bit of observed behavior, such as rateable psychiatric symptomatology, may be determined by more than a single basic factor, and certainly several different measureable patient characteristics may result from the same underlying factor. To the extent that several measureable patient characteristics reflect a single underlying factor which exists at different levels in different individuals, these characteristics will tend to co-vary (or to be correlated). That is, an individual who is high on the underlying factor will tend to have high scores on the several characteristics reflecting that factor, and individuals who are low on the factor will have low scores on these same characteristics. It is through identification of sets of patient characteristics which tend to co-vary that factor analysis leads to inferences concerning the nature of primary sources of variance responsible for this co-variation. Thus, factor analysis is a methodology for the study of individual differences. The co-variation or correlation of symptom measures depends upon the fact that they reflect underlying factors which exist at different levels in different individuals.

* The author was a member of the staff of the Veterans Administration Central NP Research Laboratory at the time that work on this project was commenced. Analysis of the data and completion of the project were supported in part by a Faculty Research Grant from Kansas State University and in part by Grant MYP-5144, National Institutes of Mental Health.

METHOD OF PROCEDURE

The first step in the research involved identification of symptom measures which can be considered to be specifically related to the clinical depression syndrome. A "manifest depression scale" was constructed to measure changes in the overt symptomatology of depression for the practical purpose of evaluating the relative therapeutic effectiveness of anti-depressant drugs (OVERALL *et al.*[1]). The scale was constructed using the expert judgment of twenty experienced psychiatrists and clinical psychologists. Each judge was asked to select from among 93 items of a depression augmented version (15 added items) of the Inpatient Multidimensional Psychiatric Rating Scale (LORR *et al.*[2]) those items which were judged to be most relevant to the psychiatric concept of depression as a symptom syndrome*. Thirteen or more of the twenty judges (two-thirds of the total) selected as relevant each of the 31 rating measures chosen for inclusion into the manifest depression scale.

Since each of the 31 measures selected for inclusion into the manifest depression scale was judged by clinical experts to be relevant for the problem of distinguishing depressed patients from normals, the present investigation was not primarily concerned with the diagnostic significance of measures†. The object of the investigation was to determine the nature of primary sources of variance which can be postulated to account for major individual differences in the symptomatology of a group of patients, all of whom have major psychiatric diagnoses of depression.

Psychiatric ratings for 204 hospitalized depressed patients were obtained in Project 5 of the Veterans Administration Cooperative Studies of Chemotherapy in Psychiatry‡. Each patient was interviewed by a clinical team of one psychiatrist and one clinical psychologist, or in some cases by two psychiatrists. Following the interview, the two observers independently completed the full 93 item, augmented IMPS. The 31 critical items were abstracted and ratings by the two independent raters were combined to yield measures with increased reliability.

The patient sample included 115 neurotic depressive reactions; 10 manic depressive reactions; 22 psychotic depressive reactions; 23 involutional psychotic reactions, depressed type; 34 schizophrenic reactions, schizo-affective type, depressed.

Ratings on the depression measures were intercorrelated to yield a 31×31 matrix of intercorrelations which was then subjected to a complete centroid factor analysis and an orthogonal normalized varimax rotation§.

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* The IMPS is a revision of the earlier Lorr Scale. For use in this depression study, 15 items which were judged to be specifically relevant to the problem of evaluating depression were added.

† Data were collected by psychiatrists and psychologists in more than 30 Veterans Administration Hospitals throughout the country in connection with a large scale controlled study of chemotherapy in depression. Primary credit for the present research, as well as for the success of the drug study, should go to these many conscientious investigators.

‡ Although the primary aim of this research was not development of a quantitative approach to the diagnosis of depression, it should be stated that this investigation is part of a larger research program ultimately concerned with the development of classification procedures. Preliminary to the development of such procedures it is necessary to identify a basic set of symptom dimensions which will prove useful in characterizing individual differences among a variety of types of psychiatric patients.

§ The author is indebted to Professor NAVARRO of Texas A and M College for the IBM 650 computer program used in the data analysis.

VOL.
1
1962/

RESULTS

Table 1 presents the substance of the 31 rating scale measures selected by the expert judges as being highly related (either positively or negatively) to the psychiatric syndrome of depression.

TABLE 1. THIRTY-ONE DEPRESSION MEASURES

1. Rate of speech slowed, deliberate, or labored.
2. Preoccupied with physical health.
3. Rate of speech hurried, accelerated, or pushed.
4. Elevated mood, sense of well-being, euphoria.
5. Blames, criticizes, condemns himself.
6. Demeanor of self-importance, superiority, conceit.
7. Body movements slowed, deliberate, labored.
8. Voice loud, boisterous, intense.
9. Anxious, uneasy, apprehensive about specific things.
10. Anxious, apprehensive about vague unknown events.
11. Demeanor of self-depreciation, inadequacy, or inferiority.
12. Downcast, depressed, dejected in feeling or mood.
13. Feelings of guilt, shame or remorse.
14. Voice low, weak, whispered, difficult to hear.
15. Overtalkative.
16. Dominant, controlling, or directive to interviewer.
17. Suicidal thoughts and impulses.
18. Delusions of unworthiness, sinfulness, evilness.
19. Delusions body is diseased, distorted, undergoing change.
20. Preoccupation with death, self-destruction, personal disaster.
21. Ruminates about hopelessness of future.
22. Ruminates about own helplessness.
23. Ruminates about personal failures.
24. Concerned over impairment in intellectual functioning.
25. Cannot work, cannot get started, loses interest.
26. Cannot make decisions.
27. Loss of appetite.
28. Loss of ability to sleep.
29. Loss of weight.
30. Loss of sexual potency.
31. Complains about general fatigue.

The complete centroid analysis resulted in a total of nine common factors being extracted*. The loadings of the 31 measures on these 9 unrotated centroid factors are presented in Table 2.

Following the normalized varimax rotation, only 8 of the factors had sufficiently high loadings to be considered for interpretation. The ninth factor had one loading of 0·44 and no other loadings exceeding 0·25; consequently it was dropped from further consideration.

Examination of loadings on the remaining eight factors indicated another problem. In construction of the IMPS, Lorr and associates avoided the use of bipolar scales. Thus, in one area, excitement-retardation, scales ran from normal to pathological in two directions. For example, consider the two scales "rate of speech slowed, deliberate, or labored" and

* The procedure which was employed used the highest correlation of a variable with any other variable as the estimate of communality.

Table 2. Unrotated centroid factors

	I	II	III	IV	V	VI	VII	VIII	IX	h^2
1.	0·54	−0·44	0·36	0·29	0·32	0·11	0·10	0·06	0·02	8274
2.	0·14	0·29	−0·33	−0·08	0·31	−0·35	0·18	0·32	0·11	5845
3.	−0·33	0·70	0·24	0·23	0·16	−0·12	0·05	−0·09	−0·05	7625
4.	−0·41	0·20	0·05	0·03	0·04	0·14	0·10	0·20	0·08	2891
5.	0·45	0·22	0·49	−0·17	−0·05	0·35	0·13	−0·11	−0·10	6839
6.	−0·26	0·48	0·22	0·28	0·14	0·15	−0·13	0·16	−0·09	5175
7.	0·59	−0·35	0·31	0·37	0·30	−0·08	−0·04	0·09	0·07	8146
8.	−0·32	0·53	0·02	0·13	0·23	−0·11	0·08	−0·14	−0·13	5085
9.	0·40	0·15	0·22	−0·17	−0·09	−0·15	0·06	−0·22	0·30	4324
10.	0·57	0·08	0·22	−0·05	−0·20	−0·28	0·26	−0·24	−0·03	6267
11.	0·63	0·06	0·52	−0·17	−0·03	0·08	0·12	0·08	0·10	7379
12.	0·69	−0·02	0·25	0·13	0·04	−0·22	−0·21	−0·11	−0·20	7021
13.	0·50	0·29	0·42	−0·22	0·03	0·26	0·16	−0·09	−0·16	6867
14.	0·43	−0·50	0·25	0·29	0·24	0·18	0·05	0·06	0·17	7065
15.	−0·38	0·64	0·28	0·22	0·18	−0·12	−0·06	−0·07	0·18	7685
16.	−0·41	0·58	0·33	0·18	0·13	0·05	−0·14	−0·02	0·07	6901
17.	0·37	0·23	−0·05	−0·09	−0·11	0·05	−0·15	0·11	−0·21	2937
18.	0·38	0·07	0·18	−0·17	0·12	0·11	0·05	0·16	−0·13	2821
19.	0·12	0·09	−0·22	−0·18	0·32	−0·18	0·21	0·34	−0·06	4014
20.	0·45	0·12	0·10	−0·15	−0·13	−0·18	−0·24	0·07	−0·28	4396
21.	0·49	0·28	0·13	0·10	−0·25	−0·27	−0·30	0·09	−0·06	5825
22.	0·48	0·22	−0·08	0·22	−0·29	−0·20	−0·22	0·14	0·09	5338
23.	0·51	0·31	0·23	−0·07	−0·28	0·06	−0·10	0·17	0·24	5925
24.	0·51	0·23	−0·19	0·36	−0·30	0·08	0·21	−0·11	−0·04	6329
25.	0·47	0·28	−0·21	0·46	−0·09	0·21	0·10	0·21	0·05	6638
26.	0·59	0·24	−0·18	0·35	−0·30	0·28	0·11	−0·16	−0·02	7671
27.	0·51	0·29	−0·26	−0·19	0·32	0·05	−0·35	−0·11	0·18	7198
28.	0·37	0·16	−0·09	−0·07	0·24	0·12	−0·16	−0·29	−0·05	3597
29.	0·37	0·27	−0·28	−0·12	0·39	0·08	−0·23	−0·19	0·12	5645
30.	0·43	0·36	−0·29	0·20	0·23	0·07	0·10	−0·10	−0·14	5360
31.	0·45	0·20	−0·34	0·21	0·11	−0·13	0·18	−0·14	0·08	4896

Table 2a. Transformation matrix for orthogonal normalized varimax rotation

0·45	−0·37	0·42	0·37	0·32	−0·42	0·16	−0·23	0·05
0·30	0·72	0·24	−0·45	0·22	−0·17	0·19	−0·09	0·10
−0·40	0·37	0·52	0·40	−0·35	−0·14	−0·30	−0·21	0·05
0·54	0·37	−0·47	0·51	−0·20	−0·05	−0·20	0·13	−0·07
−0·29	0·26	0·00	0·46	0·52	0·32	0·43	0·16	−0·24
0·27	−0·05	0·45	−0·00	0·15	0·48	−0·38	0·53	0·21
0·31	−0·05	0·24	−0·01	−0·47	0·55	0·39	−0·34	−0·25
−0·05	−0·02	0·05	0·11	−0·40	−0·21	0·57	0·50	0·46
−0·03	0·03	−0·21	0·13	0·16	0·32	−0·01	−0·45	0·77

"rate of speech hurried, accelerated, or pushed". While these two measures should have near perfect negative correlation, within the limits of reliability, the negative correlations are attenuated because of reduction in the possibility for co-variation. No matter what the pathology on one scale, the rating is normal on the other. In consequence of this fact,

VOL. 1 1962/

independent factors resulted from the machine analysis to represent the opposite ends of the undimensional bipolar continuum of retardation-acceleration. In the interest of eliminating this apparent artifact, a further rotation was accomplished to obtain a single bipolar factor to represent this continuum, and the residual factor which then had no psychological interpretation was discarded. Table 3 presents the loadings of the 31 measures on the 7 rotated orthogonal factors. The difference in communality values entered in the right-hand columns of Tables 2 and 3 indicates variance which was lost in reducing the original 9 factors to the final 7 factors.

TABLE 3. ROTATED ORTHOGONAL FACTORS

	I	II	III	IV	V	VI	VII	h^2
1.	+0·01	0·24	−0·70	+0·03	0·09	−0·00	0·00	5567
2.	+0·06	−0·13	0·11	+0·09	0·09	0·71	0·16	5785
3.	+0·01	0·01	0·75	+0·08	0·03	0·05	−0·01	5726
4.	−0·25	−0·03	0·34	−0·18	−0·08	0·07	−0·18	2551
5.	+0·07	0·77	−0·02	+0·12	0·13	−0·17	0·05	6609
6.	+0·04	0·06	0·51	−0·28	0·04	−0·02	−0·03	3466
7.	+0·21	0·10	−0·66	+0·09	0·11	0·05	0·07	5173
8.	−0·08	−0·06	0·61	+0·02	0·01	0·11	0·08	4011
9.	+0·14	0·26	−0·05	+0·54	0·05	−0·03	0·16	4103
10.	+0·29	0·33	−0·17	+0·56	0·24	0·04	−0·03	5956
11.	+0·23	0·67	−0·28	+0·29	0·06	0·03	−0·01	6689
12.	+0·57	0·24	−0·35	+0·20	0·15	−0·04	0·20	6091
13.	+0·12	0·78	0·00	+0·13	0·14	−0·02	0·12	6741
14.	−0·09	0·13	−0·70	+0·00	0·08	−0·08	0·02	5282
15.	−0·04	−0·07	0·72	+0·13	−0·08	−0·01	0·03	5492
16.	−0·03	0·03	0·69	−0·05	−0·11	−0·11	0·00	5046
17.	+0·37	0·26	0·02	−0·10	0·20	0·08	0·15	2838
18.	+0·15	0·44	−0·15	−0·05	0·03	0·17	0·08	2773
19.	−0·01	0·04	−0·05	−0·07	−0·02	0·62	0·06	3975
20.	+0·58	0·27	−0·08	+0·03	0·03	0·06	0·11	4332
21.	+0·68	0·12	0·02	+0·16	0·20	−0·00	0·08	5492
22.	+0·54	−0·04	−0·05	+0·13	0·38	0·05	0·07	4644
23.	+0·36	0·40	0·00	+0·21	0·28	−0·01	0·05	4147
24.	+0·18	0·09	−0·07	+0·16	0·75	−0·03	0·00	6344
25.	+0·14	0·06	−0·05	−0·12	0·73	0·14	0·05	5951
26.	+0·15	0·20	−0·09	+0·08	0·81	−0·17	0·13	7789
27.	+0·20	0·13	−0·03	+0·05	0·13	0·17	0·77	6990
28.	+0·07	0·19	−0·05	+0·06	0·13	−0·04	0·52	3360
29.	+0·03	0·07	0·02	+0·03	0·14	0·17	0·72	5740
30.	+0·07	0·10	0·05	−0·01	0·52	0·24	0·38	4899
31.	+0·06	−0·07	−0·08	+0·24	0·50	0·26	0·29	4742

An attempt has been made to identify the primary unitary source of variance represented by each of the rotated orthogonal factors. The 7 factor variables appear adequately characterized as (a) depression in mood, (b) guilt, (c) anxiety, (d) psychomotor retardation, (e) subjective experience of illness, (f) abnormal preoccupation with physical health, (g) physiological reaction to stress. Table 4 presents the content of measures with high loadings on each of the factors.

TABLE 4. VARIANCE SOURCES REPRESENTED IN SEVEN DEPRESSION FACTORS

I Depression in Mood
- 12. Downcast, depressed, dejected in feeling or mood. (+0·57)
- 20. Preoccupation with death, self-destruction, personal disaster. (+0·58)
- 21. Ruminates about hopelessness of future. (+0·68)
- 22. Ruminates about own personal helplessness. (+0·54)

II Guilt
- 13. Feelings of guilt, shame or remorse. (+0·78)
- 5. Blames, criticizes, condemns himself. (+0·77)
- 11. Demeanor of self-depreciation, inadequacy, or inferiority. (+0·67)
- 18. Delusions of unworthiness, sinfulness, evilness. (+0·44)
- 23. Ruminates about personal failures. (+0·40)

III Psychomotor Retardation
- 1. Rate of speech slowed, deliberate, or labored. (−0·70)
- 3. Rate of speech hurried, accelerated, or pushed. (+0·75)
- 6. Demeanor of self-importance, superiority, conceit. (+0·51)
- 7. Bodily movements slowed, deliberate, labored. (−0·66)
- 8. Voice loud, boisterous, intense. (+0·61)
- 14. Voice low, weak, whispered, difficult to hear. (−0·70)
- 15. Overtalkative. (+0·72)
- 16. Dominant, controlling, or directive to interviewer. (+0·69)

IV Anxiety
- 9. Anxious, uneasy, apprehensive about specific things. (+0·54)
- 10. Anxious, apprehensive about vague unknown events. (+0·56)

V Subjective Experience of Impairment in Functioning
- 24. Concerned over impairment in intellectual functioning. (+0·75)
- 25. Can't work, can't get started, loses interest. (+0·73)
- 26. Can't make decisions. (+0·81)
- 30. Loss of sexual potency. (+0·52)
- 31. Complains about general fatigue. (+0·50)

VI Abnormal Preoccupation with Physical Health
- 2. Preoccupied with physical health. (+0·71)
- 19. Delusions body is diseased, distorted, undergoing change. (+0·62)

VII Physical Response to Stress
- 27. Loss of appetite. (+0·77)
- 28. Loss of ability to sleep. (+0·52)
- 29. Loss of weight. (+0·72)

DISCUSSION

Among patients, all of whom are depressed, any general depression factor is minimized.[3] By reducing the general correlation between depression measures through the selection of patients, the opportunity to observe basic dimensions of individual difference among depressed patients is afforded. Seven psychologically meaningful dimensions of individual difference in depressive symptomatology have resulted.

The factor dimensions obtained in this analysis of data from a sample of hospitalized depressed patients agree very closely with independent sources of variance which have

VOL. 1 1962/

previously been identified in the analysis of psychiatric ratings of schizophrenic patients. In analyses of data from schizophrenic patients factors associated with depression in mood, anxiety, guilt, retardation and somatic complaints have been identified.[4–7] In fact, on the basis of previous analyses, a Brief Psychiatric Rating Scale has been developed with a single measure to represent each of several relatively independent factor areas previously identified, and the five factors mentioned are found included among the symptom constructs rated.[4, 5*]

It appears important from the point of view of developing a conceptual framework for characterizing psychiatric symptomatology that certain basic factor dimensions appear in various different types of patients. The reproduceability of factors across patient populations simply indicates that certain measures tend to co-vary in a variety of types of patients; it does not mean that the average *level* of pathology in the several factor areas is constant across patient populations. Thus, replicated factor dimensions which can be reliably evaluated are available for characterizing differences among different types of patients, as well as differences among patients within the several diagnostic categories.

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1
62/63

SUMMARY

A complete centroid factor analysis and normalized varimax rotation were undertaken on 31 measures of symptomatology commonly associated with depression obtained on a sample of 204 hospitalized depressed patients. Factors characterized as depression in mood, guilt, anxiety, psychomotor retardation, abnormal preoccupation with physical health, subjective experience of illness, and physical response to stress were identified. These factors correspond closely to similar factors identified in the analyses of psychiatric ratings for hospitalized schizophrenic patients.

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* Since publication of these earlier studies, the Brief Psychiatric Rating Scale has been revised and two additional symptom constructs have been included. Description of the revised scale is provided in another article[8].

VOL.
1
1962/

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RESPONSE-TIMES OF SCHIZOPHRENICS IN A PERCEIVED VELOCITY TASK

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VOL.
1
962/63

A VARIABLE such as the perceived velocity of a moving stimulus is usually assessed by procedures depending appreciably upon the subject's ability to understand and make judgments about the variable. Schizophrenic subjects present a particularly difficult problem in such perceptual tests, since deviant results might be due basically to disturbances in language and thought rather than in perception. Recently a method has been developed with normal subjects in which response-time is taken as a measure of perceived velocity[1–3] and no communication with the subject about this specific variable is required. In an exploratory application it was found that schizophrenic patients could perform the task well but developed extraordinarily long response-times with repeated testing. The present report describes an experimental verification of this phenomenon and demonstrates that the long delays are not due simply to a general deterioration in performance.

METHODS

Perceptual velocity test

From a distance of 2 m the subject viewed a light-gray trans-illuminated surface in front of an aperture through which a bright test-line rotated (Fig. 1). A ready-signal was given

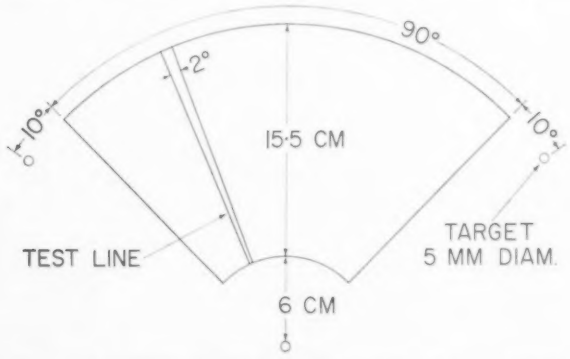

FIG. 1. Perceptual velocity aperture. Additional target spots were located at various angular distances from the edges of the aperture.

2 sec prior to the appearance of the test-line, and at the same time the designated target-spot was lighted. The subject was instructed to depress a response key when the line came into view, hold the key down while the line traversed the aperture and disappeared, and release the key when he thought the line had reached the target spot. Coincidence of test-line and target was stressed in defining the subject's response, with no explicit mention of judging speed or time. On some trials rotation was clockwise with the target on the right; on other trials rotation was counterclockwise with the target on the left. Release of the response key extinguished the target light. The pivot point was always lighted, but otherwise only the large homogeneous surface and its surround were visible between trials. No attempt was made to get these subjects to maintain fixation upon any specific point, and no knowledge of results was given.

Response-time was measured as the elapsed time from the disappearance of the test-line to the release of the response key. This response-time is not a simple reaction time, and it is possible to obtain zero or negative scores (release of the key at or before disappearance of the test-line). In this case, however, the subject was required to hold the key down until the line disappeared, and occurrences of zero or negative values were treated as mistrials.

VOL.
1
1962/

Schedule

In the exploratory experiment two speeds were used, 65 and 130°/sec angular velocity of the test-line, and two target distances, 110° and 230° beyond the edge of the aperture. Additional trials with targets at 50°, 80°, and 180° were included in order to obtain greater variation in the correct response-time values, but these additional trials were not recorded. Alternating with the perceptual velocity trials were simple reaction-time determinations: A stationary light came on 1·75 sec following a tone-signal and remained on for 2 sec. The subject was required to depress his response-key while the light was on and release the key as soon as possible after the light went off.

The schedule was changed considerably for the main experiment. Five speeds — 22·5°, 30°, 40°, 53·3°, and 71·1°/sec — and six target distances — 10°, 20°, 30°, 60°, 70°, and 80°— were presented, making 30 different speed-target combinations with correct response-times ranging from 0·14 to 3·56 sec. No simple reaction-time scores were obtained.

For all subjects the sequences of trials were partly random but balanced so that the various conditions occurred early and late in a session, and followed each other about equally often. All subjects completed thirteen sessions, one per week on the average.

Subjects

All schizophrenic subjects were chronic hospitalized patients. In the exploratory experiment 6 male patients were selected as the most likely of a small group (described in detail by PERLIN and LEE[4]) to be able to perform the experimental task. These individuals were already participating in an extended drug study.[5] Although the drugs had no demonstrable effect on the performance studied here, this was none the less a rather special group.

In the main experiment 42 schizophrenic patients of varied diagnostic subtype were selected solely on the basis of availability for the experiment and freedom from complicating

neurological disease. Seven were unable to meet the minimal task criterion of holding the response key down while the test-line was visible and releasing it after the test-line had disappeared. The main experimental group was comprised, therefore, of 35 patients, 19 male and 16 female, 19 to 52 years old, having 4 to 16 years of education. These patients were taken off all medication for two weeks preceding the testing and during the testing period.

The control group consisted of 23 students, office personnel, nurses, and doctors, 10 male and 13 female, aged 22 to 52. No prior matching of control and experimental subjects was attempted, but it was possible to equate one group of schizophrenics with the controls on the basis of a response criterion (explained later).

Additional observations

All patients were rated by the experimenter for cooperativeness. This rating consisted essentially of an overall judgment as to how difficult it was to get the individual to come to the experimental room, start the task and keep at it for the required number of trials. The attempt was to rate apparent willingness rather than capacity to perform.

Patients in the main experimental group were also interviewed by two psychiatrists, who completed a symptom check list for each patient. The items were specifically relevant to the symptomatology of chronic schizophrenic patients and are described by WALDROP *et al.*[6]. One special item was added; viz., "tendency toward self-preoccupation."

EEG records were taken on the patients in the main experimental group during the thirteenth session while the subject was performing the perceptual velocity task. Two unipolar leads were used, one occipital and one frontal, both placed slightly to the left of the midline. These records were examined grossly by two experienced EEG investigators, without identification of the patients and without knowledge of any results on the perceptual task, for evidence of failure to show alpha-blocking during the time the test-line was in view.

RESULTS

In the exploratory experiment 5 of the 6 subjects developed increasingly longer response-times as the testing progressed. The sixth subject did not clearly constitute an exception, because his response-times tended to increase for several weeks, drop back suddenly to the initial level, and then increase again for several weeks. Simple reaction time remained at approximately the same level for each subject throughout. The mean values for all conditions are shown in Fig. 2. Since the response-times were longer than the corresponding correct response-times to begin with, the increase constitutes an increase in absolute error. An analysis of response-time as a function of speed and target distance, however, suggested a high degree of *relative* accuracy in spite of the large constant errors. This matter was investigated more extensively in the main experiment.

The product-moment correlation coefficient between observed response-time and correct response-time was computed for each subject in the main experiment.* This measure

*For statistical analyses the correlation coefficients were transformed to z-scores. Significance of differences for all measures reported in this paper was evaluated by means of the t-test; wherever variances were significantly different, Welch's modification was used.[7]

reflects the degree to which variation in the subject's response-time was related to variation in the parameters of the task. Since a number of the 30 different speed-target combinations required approximately the same correct response-times, they were averaged together yielding 17 different correct response-time values. The corresponding subjective response-times were averaged over the entire period of testing for each subject. An *a priori* criterion

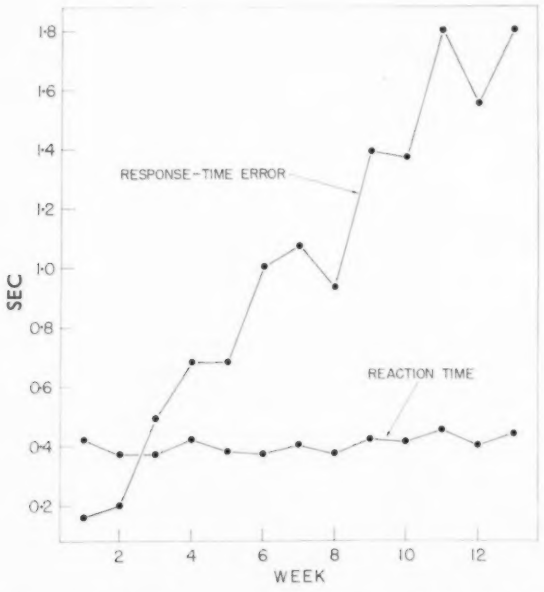

FIG. 2. Perceptual velocity response-time error (observed minus correct response-time) and simple reaction time for 6 schizophrenic patients in the exploratory experiment (average correct response-time = 1·96 sec).

of statistical significance at $p = 0{\cdot}01$ ($r = 0{\cdot}61$) was established as representing the minimum acceptable level of competence in performing the task. Of the 35 schizophrenics 3 failed to meet this criterion, and their data were not used in any further analyses.

The correlations for the control group were all essentially perfect ($r \geq 0{\cdot}97$). Half of the 32 schizophrenic subjects achieved values at least that high (referred to as Group I), while half had values lower than 0·97 (Group II). Group I, therefore, can be considered to be matched with the control group with respect to relative accuracy of performance. The average correlation for Group II was 0·90 which is significantly lower than the average for the controls but still represents a fairly high level of competence in performing the task.

In order to test whether it was the poorer performers who developed longer delays in response, the course of the response-times was plotted separately for Groups I and II (Fig. 3). Here again, all response-times were too long to be correct in an absolute sense, so that an increase in response-time represents an increase in absolute error. On the average, however, Group I, whose performance was better in terms of relative accuracy, tended to manifest progressively longer response-times, whereas Group II paralleled the control group.

A straight line fits the averaged data for the first ten weeks very well, and reasonably well in each individual case, so the slope of the best-fitting straight line for the first ten weeks was calculated for each subject as a measure of his tendency to develop lengthened response-times. These slopes were more heterogeneous for the schizophrenics than for the controls, and the distributions for both Group I and Group II include the distribution for controls.

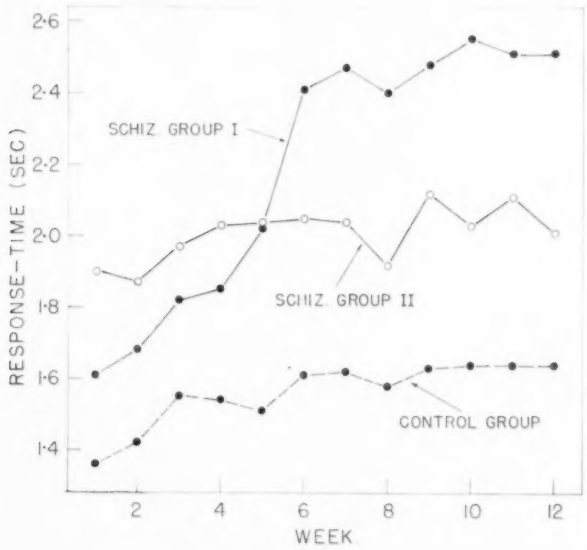

FIG. 3. Perceptual velocity response-times for 32 schizophrenic patients (16 in each group) and 23 control subjects (average correct response-time = 1·22 sec).

Consequently the mean of the slope values and the mean of the final response-time levels (average of weeks 11 and 12) for Group I were different from the corresponding values for the control group at only a borderline level of significance ($p \sim 0{\cdot}10$). In addition, for the entire group of 32 schizophrenics the correlation between slope score and relative accuracy was 0·32 ($p \sim 0{\cdot}10$), and the correlation between slope score and initial absolute error (week 1) was essentially zero. Thus, although it is clear that the subjects developing lengthened response-times were not those who performed less well generally, the positive association between lengthened response-time and quality of performance was slight.

Ten of the patients had slope values exceeding the highest slope of any individual in the control group. Six of these were members of Group I, four of Group II. The correlation between observed and correct response-times was computed separately for each quarter (three-week period) for each of these 10 subjects. The average coefficients were 0·95, 0·94, 0·96, and 0·95, respectively, for the first through fourth quarters. No decrease in relative accuracy accompanied the marked increase in response-time, even for the individuals showing the very longest delays. The most extreme subject waited an overall average of 8·45 sec during the fourth quarter, an average absolute error of 7·23 sec (nearly 600 per

cent), and yet the correlation between his response-times and the correct response-time values was 0·98 for the same period. Also for these 10 subjects, the slope of the function relating observed response-time to correct response-time increased over the four quarters (1·69 to 2·81, on the average); that is, a constant increment did not accrue indiscriminately to all responses, but rather the increments tended to be proportional to the correct response-time values.

Additional analyses were undertaken for all subjects to determine whether they tended to discriminate target distances more accurately than speeds (or vice-versa) and whether response-time errors tended to be different, or to change differently over time, for the longer correct response-time conditions as compared to the shorter correct response-time conditions. In general, speeds and target distances were discriminated about equally well, and changes in per cent error over the weeks were not associated more with the longer correct response-time conditions than with the shorter correct response-time conditions.

From inspection of the EEG records 11 patients were selected as exhibiting failure of alpha-blocking during presentation of the perceptual velocity stimulus. The expectation was that these subjects would be the ones who had developed the long response-times over the course of the testing (high slope group). The patients giving evidence of alpha-blocking, plus a few for whom no alpha-frequency was discernible at all, constituted the comparison group. This differentiation on the basis of the EEG was associated with a clearly significant difference in average slope score (Table 1), although 4 individuals with moderately high

Table 1. Perceptual velocity performance of schizophrenic patients differentiated on the basis of EEG

Prediction from EEG	Measure	Relative Accuracy*	Slope
High Slope Group	Mean	2·14	0·195
(N = 11)	S.D.	0·72	0·222
Comparison Group	Mean	2·01	0·001
(N = 21)	S.D.	0·67	0·111
	P	n.s.	0·01†

*z-transformation of correlation between correct and observed response-times.
†Single-tailed probability derived from Welch's t-test for the difference between means with unequal variances.

slope values were misassigned to the comparison group. The average slope for the high slope group was also significantly different from the average (0·027) for the control subjects ($p \sim 0{\cdot}02$). A later check on 19 of the patients revealed no relationship between slope score and per cent-time alpha obtained before and after an experimental session. No abnormal

VOL. 1 1962/

discharges were noted in any of the EEG records, but special procedures for eliciting such discharges were not employed.

Age, sex, education, duration of hospitalization, cooperativeness, and ratings on the symptom checklist were all unrelated to slope score. In view of this failure to be able to characterize the patients who developed the longer delays in response, a careful review of the hospital records and a special psychiatric interview of the patients were undertaken. This analysis was done with full knowledge of the subjects' performances on the experimental task. Even so, it was not possible to arrive at any clear differentiation between high- and low-slope subjects with respect to personality or particular features of psychopathology.

Finally, a determination was made of the fewest testing sessions necessary to predict the overall slope-score based on ten weeks. As already mentioned, the correlation between overall slope and initial response-time level was practically zero. The correlation with the difference in response-time between the first and second sessions was significant but of insufficient predictive value ($r = 0{\cdot}54$, $p < 0{\cdot}01$). It was necessary to compute a slope score for six or more sessions in order to achieve a correlation of 0·90 or higher.

OL.
1
62/63

DISCUSSION

The initial experiment suggested that progressively increasing response-time in this experimental situation might be characteristic of all, or nearly all, schizophrenics. Probably the most non-representative feature of those first subjects was that they had been, and were being, tested a great deal on psychological and other experimental procedures. In any event, the more adequate later sample would suggest that only about one-third of the schizophrenics able to perform the task show the effect clearly and they do not represent any obvious particular aspect of schizophrenia. Moreover, we have tested many normal subjects on this experimental task in addition to the present subjects, and the great majority have manifested some increase in response-time under repeated testing. It would seem appropriate, therefore, to characterize the marked increase in response-time shown by some of the schizophrenics as an exaggeration of a normal tendency rather than a qualitatively different phenomenon.

There are several avenues to pursue in seeking an explanation which would postulate a quantitative effect on an essentially normal process. First, since response-time in this test is a function of perceived velocity, a decline in the apparent speed of the test-line might be responsible for the increase in response-time. Perceptual adaptation to motion is an established fact, though it is usually demonstrated by a temporary after effect following immediately upon a period of continuous stimulation (the so-called waterfall illusion is a common example). If the week-to-week changes observed here were the result of perceptual adaptation, it would have to be an adaptation effect conditioned specifically to the test situation. Such conditioning may be possible, but, aside from a number of technical difficulties, adaptation is presumably a very basic aspect of perceptual functioning and the effect should at least be consistent among those subjects performing the task well. Actually, 6 of the patients whose performance was perfectly competent showed a slight *decrease* in response-time. Thus, although we cannot rule this hypothesis out altogether, some other possibilities seem more likely.

The most obvious general concomitant of repeated testing is an increase in tediousness for the subject. At first the task is novel, perhaps even threatening for some schizophrenics, but it becomes routine and boring with many repetitions. It would be entirely reasonable for subjects to become less and less specifically alert to the task, and the EEG findings lend support to this possibility. Also, attentional factors are typically associated with large individual differences among subjects, and some schizophrenics do not seem to become bored with simple repetitious tasks which severely try the patience of others. One cannot, however, postulate just a general decrease in vigilance as underlying the increased response-time, for there was no accompanying deterioration in relative accuracy. If the subject were simply no longer paying attention to the task, the quality of his performance should suffer in all respects.

A third possibility, related to the second, involves the perception of time. Operationally, the subject's task is to allow an appropriate interval of time to elapse between disappearance of the test-line and release of the response-key. LOEHLIN[8] has found the major factors relating to the subjective passage of time to be interest vs. boredom, filled vs. empty intervals, repetition, and activity vs. passivity. Changes in these variables are clearly possible over an extended period of repeated testing on the same task. Moreover, FALK and BINDRA[9] found that with repeated trials (in this case within a single session) normal subjects equated longer and longer intervals of elapsed time to a stated standard of 15 sec. If perceived speed of the test-line can be assumed to be independent of perceived duration, then a progressive time contraction would offer a straightforward basis for increasing response delays in the present situation.

GERHARD,[1] however, has emphasized the possible dependence of apparent speed upon apparent duration. One might suppose that if the test-line seemed to take longer to traverse a given distance it would appear to be moving more slowly, or if it seemed to take less time it might appear to be moving faster. But such an effect could not lead to a change in response-time. Following disappearance of the stimulus a given objective time-interval would, equally, seem longer or shorter, resulting in no effect on the subject's overt response-time. An alteration in the experience of time rather than velocity thus appears to provide a plausible working hypothesis for further investigation of the abnormal increase in response-times demonstrated in the present study.

The effect with which we have been concerned is a shift in response-time independent of the subject's absolute starting level. Whether this effect is related to a more general distortion in time sense, often attributed to schizophrenics, is problematical. DOBSON[10] found that neither time-oriented nor time-disoriented schizophrenics differed significantly from normal subjects in their mean estimates of relatively short time-intervals. Others have obtained a tendency for schizophrenics to overestimate the duration of short intervals.[11–13] Our patients generally exhibited longer response-times than our controls, which would be consistent with time underestimation rather than overestimation. The determination of absolute under- or overestimation, however, depends upon the subject's concept of a unit of measurement, such as a second or a minute, and need not necessarily be related to the functional use of time in a task not requiring estimates in terms of such units.

VOL.
1
1962/

SUMMARY

Forty-one chronic schizophrenic patients were tested over a number of weeks on a perceptual velocity task in which response-time is correlated with the speed of a moving stimulus. Fifteen of the patients developed remarkably long absolute response-times but maintained a high degree of relative accuracy. This tendency was significantly related to absence of alpha-blocking in the EEG but not to specific symptomatology or other individual characteristics. Tentatively, the phenomenon is interpreted as an exaggeration of a normal change in the perception of time-intervals under repeated testing on the same task.

OL.
1
62/63

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The subjects in the main experiment were patients at Saint Elizabeth's Hospital. We are grateful to Dr. WINFRED OVERHOLSER, Superintendent, for his cooperation in making patients available for the prolonged period of testing required.

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VOL.
1
1962/

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EARLY EFFECTS OF CHLORDIAZEPOXIDE (LIBRIUM) USED WITH PSYCHOTHERAPY*

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INTRODUCTION

THE broad aim of the study was to determine some of the early effects of an ataractic agent, chlordiazepoxide, on anxiety and tension. Typically such drugs are prescribed as an adjunct treatment in neurosis for the purpose of relieving patient distress likely to interfere with psychotherapy. The problem was whether a drug so used results in more anxiety reduction than psychotherapy given alone. A related problem was to ascertain the effects of an ataractic administered with psychotherapy as compared to its effects when given alone. There are clinics operating in which psychotropic drugs are used as primary treatment and often in the absence of psychotherapy. A third problem concerned the pattern of treatment effects over time for groups receiving different combinations of treatments. For example, the action of the drug alone over a four-week period might be expected to be different from the effects of placebo given alone, or of the two medications when combined with psychotherapy. There was also the interesting question as whether the tranquilizer interferes with therapy. The study was designed to answer these and related issues.

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EXPERIMENTAL DESIGN

The research may be described as a four-week double-blind study of the effects of chlordiazepoxide on a group of 150 male outpatients newly accepted for individual psychotherapy. Patients selected for the study were randomly assigned in each of 23 Veterans Administration Mental Hygiene Clinics to six treatment groups receiving the combinations of psychotherapy and medication shown in Table 1. All medication* (chlordiazepoxide and

TABLE 1. THE EXPERIMENTAL DESIGN

	Librium (Li)	Placebo (Pl)	No Med.
Psychotherapy (Ptx)	Li and Ptx	Pl and Ptx	Ptx Only
	n = 25	n = 25	n = 25
No Psychotherapy	Li	Pl	Wait
	n = 25	n = 25	n = 25

placebo) was prescribed by a physician for four weeks under double-blind conditions. Dosage of the medication was fixed for the first week, individually adjusted when necessary at the end of the first and second weeks, and fixed at the individual's optimal level for the remaining two weeks.

The specific research hypotheses tested were that there would be a greater reduction in anxiety and tension;

1. in groups receiving psychotherapy than those without psychotherapy;
2. in groups receiving chlordiazepoxide than those receiving placebo;
3. in groups receiving some medication than in groups receiving no medication.

Similar hypotheses were tested for other patient and therapist criteria such as somatic and psychic distress, hostility, fatigue, lack of vigor, thinking confusion, depression, severity of illness, and physical complaints. Since relatively little is known concerning the specific action of tranquilizers it seemed best to include a variety of measures which might plausibly reflect drug effects.

The patient sample

Any male veteran regarded as acceptable by the clinic for intensive individual psychotherapy given once a week for 50 min could be included. Patients with the following characteristics were excluded: 1. those who had been hospitalized for a psychiatric illness during the previous three months; 2. those who had been in group or individual psychotherapy anywhere during the previous three months; 3. those with a history of central nervous system disorders or seizures; 4. those with symptomatic addiction to alcohol; 5. those who could not discontinue medication while in the study; 6. those 55 years of age

*Hoffman-LaRoche Laboratories, Inc., Nutley, New Jersey, generously prepared and furnished all medications.

VOL.
1
1962/

or over. The data collection period extended from January through September 1961, but the bulk of cases were collected prior to July of 1961.

The clinic investigators (CI) were instructed to select a random sample of those patients ordinarily chosen for psychotherapy given once or twice a week. The CIs were also provided with a list of code numbers. Once a patient was selected he was assigned the next unused code number. The CI then opened a sealed envelope, with the same code number, that contained a slip indicating the group to which the patient was to be assigned. The code numbers had been randomly allocated by the authors to one of the six possible treatment groups. As far as could be determined CIs adhered closely to the above procedures. At no time were patients informed that they were participating in a research project.

As may be seen in Table 2 a total of 311 cases were actually assigned to the project. Of this group 181 satisfied all criteria while 130 failed to fulfil all requirements. Thirty-one

OL.
1
62/63

TABLE 2. NUMBER OF CASES ASSIGNED TO STUDY SATISFYING AND NOT SATISFYING CRITERIA

	Treatment Group						
	Ptx and Li	Ptx and Pl	Ptx	Li	Pl	Wait	Total
Satisfying all criteria	28	30	27	30	28	38	181
Included in analysis	25	25	25	25	25	25	150
Eliminated randomly or arrived late	3	5	2	5	3	13	31
Not satisfying criteria	26	25	26	19	19	15	130
Did not return, etc.	14	8	11	7	6	7	53
Hospitalized, moved, etc.	1	3	3	2	0	3	12
Experimental deviate	11	14	12	10	13	5	65
Total assigned	54	55	53	49	47	53	311

cases were either randomly eliminated for statistical reasons (equate groups for size) or arrived too late for analysis. Of patients not satisfying study criteria 12 were hospitalized or moved to another city, 53 failed to return or refused treatment, and 65 exhibited one or more experimental deviations. Illustrative of experimental deviators are those persons who failed to take medications as required, missed more than one psychotherapy appointment, or who were not on drugs at the time of re-examination. A detailed record was kept at each clinic of all appointments kept or missed by each patient. These records as well as the prescribing physician's observations were forwarded to the research unit when a patient completed his study treatment. In addition each CI sent in a biweekly report of patients selected or dropped along with the reasons for termination or exclusion. This information and dates of test and re-test administration enabled the authors to scrutinize each case carefully and to determine whether or not all study requirements had been satisfied.

Inspection of Table 2 shows that the treatment groups did not differ with respect to the number of experimental deviates. The Wait Group is not included in this judgment as it is not comparable. Its members received no treatment and were involved in fewer appointments. On the other hand the drop out rate for all reasons is higher for groups receiving psychotherapy (25 per cent) than for those not receiving psychotherapy (17 per cent). Of

patients receiving psychotherapy 40 out of 162 terminated while of 149 without benefit of psychotherapy 25 terminated. The ratios remain about the same when cases that were hospitalized or who moved away are excluded.

The treatments

The study medication which consisted of chlordiazepoxide (Librium) in 10 mg capsules or placebo were prescribed in the following manner. During the first week all patients scheduled for medication received a total daily dosage of four capsules. In the second week the physician prescribed four capsules if adjustment was not required. When required the dosage could be lowered to three or increased to five or six capsules per day. At the beginning of the third week, dosage could be lowered to two capsules or increased to eight capsules per day. This final dosage remained fixed for a given patient for the last two weeks. Examination of the Patient Medication Records showed that 71 per cent were maintained at four capsules per day, the dosage recommended by the drug company as optimal.

Each clinic pharmacist dispensed the medication, which was delivered in individual bottles containing 250 capsules identical in size, color, appearance, and taste. Each bottle was labeled with the unique code number assigned to the patient. The identification label of the study medication sealed in small envelopes was placed in the hands of the pharmacist. Codes were not broken until after completion of the study.

Patients in three of the treatment groups received intensive individual psychotherapy, defined as 50-min interviews given once a week. In no case did the therapist also take the role of prescribing physician for the same patient. A therapist was defined as any clinic member to whom patients are ordinarily assigned for "psychotherapy".

Examination sequence

The intake social worker recorded background data during or just following the usual intake interview. Except for Wait Group patients, all patients completed an inventory on the same day or within a week of initiation of treatment, but always before the first treatment. They were administered a 10-min adjective rating scale and completed a global improvement rating just before the second, third and fourth treatment visits to the therapist or prescribing physician. Just before the fifth treatment, each patient was re-examined on a modified inventory. Since the Wait Group received no treatment for four weeks, initial testing was completed early. The adjective rating scale was given only once, a week after the initial inventory was completed. Wait Group cases then waited three weeks for a final re-testing, given prior to the initial psychotherapeutic interview. The treatment groups did not differ on the number of days between their initial and final tests.

Therapists recorded observations of their patients on a Therapist Form immediately after the first, second and fifth interviews. Wait and Medication Only groups were described only once on this form and then after the initial interview, which was scheduled to begin the day they completed their final tests. After the third or fourth interview, each therapist described his patient on the Interpersonal Behavior Inventory (IBI).[1]

The prescribing physician saw each patient once a week to initiate and replenish the study medication, to insure that the patient was adhering to the prescribed dosage, and to check on the presence of side effects. Each week he recorded his observations as to side effects and

VOL.
1
1962/

indicated the number of capsules prescribed on a Medication Check List. He also recorded his opinion of the drug and his opinion of the usefulness of tranquilizers generally before the beginning of the study.

The patient measures

Ten criteria were used as measures of change. The first two, psychic and somatic discomfort, consist of 40 somatic and psychic complaints frequently reported by patients. The patient indicated on a four-point scale the degree to which he had been distressed by each problem during the past few weeks. Six measures were based on a sixty-adjective feeling and attitude scale, which has been shown to be sensitive to change in several studies. The patient rated himself on each word, such as "anxious", by indicating how he had been feeling during the past week. For each word he checked "not at all", "a little", "quite a bit", or "extremely". The six moods measured are labeled Tension-Anxiety, Anger-Hostility, Depression, Vigor, Fatigue-Inertia, and Thinking Confusion. An eighth measure consisted of 31 specific social and psychological changes a patient may have observed in himself during the course of four weeks of treatment. On the tenth measure the patient indicated how much better or worse he felt after four weeks of treatment.

In addition, several control measures were employed. Included were: 1. a Social Desirability Scale[2]; 2. a Terminator-Remainer predictor scale of 21 items; 3. a 9-item Attitude toward Physicians scale. Data were also collected on background variables such as age, marital status, education, employment status, annual earnings, and number of prior therapy courses.

The therapist measures

Ten therapist criteria of change, as well as seven potential predictor measures, were obtained. Three were status measures based on seven-point intensity scales of Anxious Intropunitiveness, Tension and Hostility taken from an existing rating schedule.[3] Five measures were taken from an Inventory of Changes,[4] which describes specific changes likely to occur during psychotherapy. A patient received scores on Reduced Somatic Complaints, Hostility Reduction, Increased Sociability, Increased Self-other Acceptance, and Anxiety Reduction. Also included was a global estimate of the severity of the patient's illness and a global measure of over-all improvement following four weeks of treatment.

Also included were five measures of the quality of the Interview Relationship, labeled Rapport, Blocking, Hostile Resistance, Dependency, and Controlling Resistiveness. In addition, therapists indicated their therapeutic goals, which were scored as seeking personality modification or as primarily supportive. The IBI was completed by the therapist after three or four sessions and three scores descriptive of characteristic interpersonal behavior patterns were derived. Other minor measures will be described later as appropriate.

The principal procedures used to identify significant treatment effects were analysis of covariance and orthogonal comparisons based on the research hypotheses. By the covariance procedure, initial differences among groups on the various criteria were removed. The three research hypotheses were then tested on the adjusted scores by means of orthogonal comparisons.[5]

THE FINDINGS

Patient and therapist characteristics

The typical patient in the sample of 125 was a high school graduate, 37·8 years of age, who earned $3,500 a year. Of the total, 73 per cent were married, 67 per cent were employed, 34 per cent had had prior psychotherapy and 37 per cent had received prior tranquilizer treatment. Education was the only background variable in which the treatment groups differed. The Psychotherapy Only group included a higher proportion of college graduates than the Wait Group. Interpersonally, the sample can be characterized as an anxious and passive-dependent group.

The six treatment groups were compared relative to their means on initial patient criteria. No significant differences were found. The three groups receiving psychotherapy were also compared relative to their scores on initial therapist criteria and again no differences were significant. Initial therapist assessments as to patient motivation, prognosis, and ease of establishing a relationship also yielded no differences upon test.

The therapists' initial diagnosis classified 42 per cent of the total sample as Neurotics, 26 per cent as Personality Disorders, 15 per cent as Psychophysiologic Disorders, and 18 per cent as Psychotics. While there were some differences between treatment groups, these proved to be non-significant. The mean global severity of illness rating for the sample was "Moderately Ill".

Fifty-nine psychotherapists participated in the study. Fifty-six per cent of patients were seen by psychologists, 27 per cent by social workers, and 17 per cent by psychiatrists. Seventy per cent of patients were seen by staff members and the remainder by trainees and residents. The median experience of therapists was 6·5 years and 54 per cent had received some personal psychotherapy. The psychotherapy groups did not differ as to sex, profession, amount of personal analysis, or years of experience of their therapists.

The physician's report

Was the physician able to guess who was on the active drug? The physician's guess at the time of his final contact indicated that cases on the drug could not be significantly differentiated from those on placebo. However, a significantly greater than chance per cent (63) were judged to be on the drug.

How often would the physician have prescribed a tranquilizer to those receiving medication? Fifty-nine per cent of those on medication would have been given a tranquilizer. On the other hand, patients judged to need a tranquilizer were rated as being no more improved than those not needing a drug.

Patients on the active drug were rated by the physician as significantly more improved than the placebo patients ($F = 3{\cdot}48$; $p < 0{\cdot}05$). Of the Librium cases, 74 per cent were rated improved compared with 62 per cent of the placebo cases. Furthermore, patients guessed to be on the active drug were rated as significantly more improved than those guessed to be on placebo. Patients reporting medication to be helpful were significantly more often on Librium. Significantly more drug than placebo patients were continued on a tranquilizer after conclusion of the study. The evidence thus supports the presence of a statistically significant drug effect.

VOL.
1
1962/

The weekly record of side effects showed that 31 per cent reported no side effects, 46 per cent reported one or two, while 23 per cent reported three or more. The placebo and active drug groups did not differ on the incidence of over-all or single side effects. The most commonly reported complaints were drowsiness (26 per cent), insomnia (12 per cent), and dizziness (10 per cent). Evidently then 40 mg of chlordiazepoxide does not produce interfering side effects. Finally, dosage adjustments were about equally frequent for placebo and for active drug groups.

Patient self-reports

Consistent with our research hypotheses three comparisons were made of the effects of treatments on the patient criteria for the four-week period. These comparisons were: 1. the effects of psychotherapy versus the absence of psychotherapy across treatment groups; 2. the effects of the active drug versus the effects of the placebo; 3. the effects of receiving any medication versus the effects of receiving no medication. Finally a test was made to determine whether there was an interaction effect for the first comparison, i.e.,whether the effects were uniform or not across treatment groups. The results are shown in Tables 3 and 4.

OL.
1
62/63

TABLE 3. TESTS OF DIFFERENCES (*F* RATIOS) ON PATIENT CRITERIA (INITIAL SCORES CONTROLLED)

Criterion	Ptx vs. No Ptx	Li vs. Pl	Med. vs. No Med.
Somatic Discomfort‡			
Ptx Groups		4·25*	0·44
No Ptx Groups		0·44	11·02†
Psychic Discomfort	0·58	0·37	0·35
Tension-Anxiety	0·83	0·00	3·49*
Anger	0·04	0·02	1·16
Depression	0·75	0·00	3·75*
Vigor	1·86	0·24	1·40
Fatigue-Inertia§	0·80	0·46	2·52
Confusion§	0·00	0·89	1·82
Psychic and Social Changes§	1·41	1·29	10·27†
Improvement rating§	1·31	0·01	9·36†

*$p < 0.05$ (I-tailed).
†$p < 0.01$ (I-tailed).
‡Groups were analyzed separately because of a significant interaction.
§*F* tests based on analysis of variance of four-week scores.

The patient reports uniformly indicated that groups receiving psychotherapy over the four-week period of study responded no differently than groups not receiving psychotherapy. Active drug patients did no better than placebo patients. In contrast there was a "capsule effect". Capsules as compared to no capsules resulted in a greater reduction in Tension-Anxiety and in Depression. The capsule patient's global improvement ratings and his reported psychological and social changes were significantly greater. Because of the significant interaction obtained for Somatic Discomfort, separate tests were made for groups receiving psychotherapy and those not receiving psychotherapy. For the psychotherapy patients, the drug was more effective than placebo. For patients not receiving psychotherapy, a capsule was more effective than simply waiting.

TABLE 4. FOUR-WEEK ADJUSTED MEANS ON PATIENT CRITERIA

	Comparisons				
Criterion	Ptx	No Ptx	Li	Pl	No Med.
Psychic Discomfort	24·4	25·4	25·1	24·2	25·4
Tension-Anxiety	20·2	21·0	20·0	20·0	21·7
Anger	11·9	12·0	11·7	11·6	12·4
Depression	13·9	14·6	13·7	13·6	15·4
Vigor	8·3	7·6	8·3	8·0	7·5
Fatigue-Inertia*	7·6	8·1	7·8	7·3	8·5
Confusion*	7·7	7·7	7·7	7·2	8·1
Psychic and Social Changes*	7·7	6·8	8·8	7·6	5·4
Improvement Rating*	3·6	3·4	3·7	3·7	3·1
N	75	75	50	50	50

*Unadjusted four-week means are presented.

Also investigated were the first-week effects of medication. Comparison of the two drug groups with the two placebo groups revealed that Tension-Anxiety was reduced significantly more for the former during the first week of treatment. Secondly, ratings of Vigor were significantly greater for the drug groups. Thirdly, drug patients reported more global improvement than placebo patients, and the combined capsule groups reported more

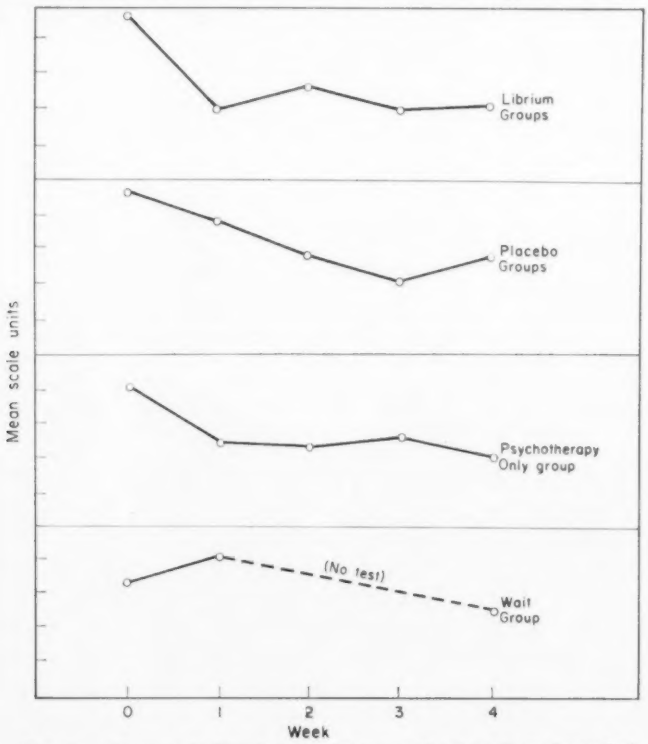

FIG. 1. Changes in Tension-Anxiety over the 5-week study period.

VOL. 1 1962/

improvement than the no-capsule groups. These findings are in agreement with clinical reports of anxiety reductions and simultaneous increase in energy level. However, the reader should note that these effects, as far as the patient was concerned, washed out by the end of four weeks.

The pattern of changes in patient ratings on Tension-Anxiety are exhibited in Fig. 1. The drug patients showed a sharp initial drop in anxiety, followed by a leveling off. Anxiety reduction in the placebo patients was proportional to time until the fourth visit and then rose. The Wait Group patients, however, reported themselves slightly worse and then leveled off.

A very similar pattern of changes is revealed in the Vigor scores (Fig. 2). The score

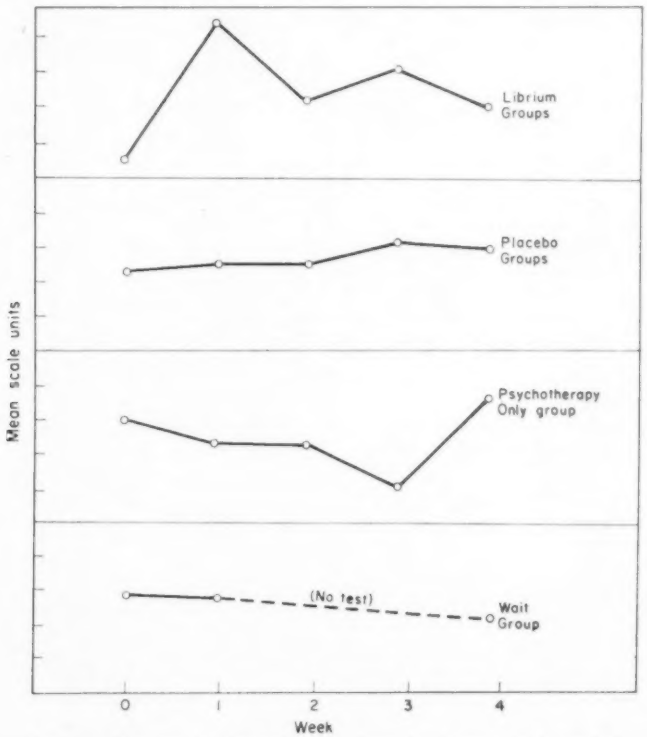

FIG. 2. Changes in Vigor-Activity over the 5-week study period.

increase in the active drug patients was sharp initially, but it fell and then leveled off. The placebo patients' pattern was one of slow increase until the fourth visit. The Wait Group showed virtually no changes. However, the Psychotherapy Only patients showed a fall in Vigor scores and a terminal increase for reasons unknown.

Therapist reports

Tables 5 and 6 present the findings on the therapist criteria for the groups receiving psychotherapy. Comparisons of the drug and the placebo groups show that severity of

TABLE 5. TESTS OF DIFFERENCES (*F* RATIOS) ON THERAPIST CRITERIA (INITIAL SCORES CONTROLLED)

Criterion	Li vs. Pl	Med. vs. No Med.
Status Ratings		
Hostile Belligerence	2·12	0·37
Anxious-Intropunitiveness	0·01	6·76†
Manifest Tension	0·82	0·54
Severity of Illness	8·28†	1·03
Interview Relationship		
Rapport	0·12	0·68
Blocking-Silence	0·06	0·03
Antagonistic-Resistive	0·06	0·02
Leading-Controlling	1·23	0·55
Ingratiating	0·20	0·01
Change Inventories		
Somatic Complaint Reduction‡	1·70	3·64*
Increased Affection-Rapport‡	3·40*	1·96
Increased Sociability‡	0·54	0·60
Hostility Reduction‡	0·58	2·01
Anxiety Reduction‡	0·87	0·02
Improvement Rating§	0·28	3·02*

*$p < 0·05$ (I-tailed).
†$p < 0·01$ (I-tailed).
‡A variable other than initial score was covaried.
§*F* tests based on analysis of variance of four-week scores.

TABLE 6. FOUR-WEEK ADJUSTED MEANS ON THERAPIST CRITERIA

	Treatment Groups		
Criterion	Ptx and Li	Ptx and Pl	Ptx only
Status Ratings			
Hostile Belligerence	8·7	11·2	9·1
Anxious-Intropunitiveness	10·6	10·7	14·3
Manifest Tension	2·6	2·9	2·5
Severity of Illness	2·4	2·8	2·8
Interview Relationship			
Rapport	8·6	8·3	7·9
Blocking-Silence	1·2	1·3	1·2
Antagonistic-Resistive	2·7	2·8	2·7
Leading-Controlling	3·6	4·6	3·5
Ingratiating	4·0	4·3	4·2
Change Inventories			
Somatic Complaint Reduction*	1·7	1·3	1·0
Increased Affection-Rapport*	2·4	1·3	1·2
Increased Sociability*	0·9	0·7	0·6
Hostility Reduction*	2·1	1·7	1·3
Anxiety Reduction*	4·0	3·2	3·7
Improvement Rating*	2·1	2·1	1·8
N	25	25	25

*Unadjusted four-week means are presented.

VOL. 1 1962/

illness was significantly less in the drug group after four weeks and that judged expression of affection and rapport with others was significantly greater. The next contrast is capsules versus no capsules. Here, Anxious Intropunitiveness and Physical Complaints were significantly more reduced in the groups receiving capsules. The mean global rating of improvement was also higher in the capsule groups.

Pre-post changes

The pre-post changes over the four-week period for patient criteria were tested for what light they might shed on the findings as a whole. The results are presented in Table 7. Most noteworthy is that the Wait Group was the only group showing no significant changes and

TABLE 7. SUMMARY OF PRE-POST CHANGES (*t* TESTS) ON PATIENT CRITERIA

	Group					
Criterion	Li and Ptx	Li	Pl and Ptx	Pl	Ptx Only	Wait
Somatic Discomfort	++	+	0	++	++	−
Psychic Discomfort	++	++	++	++	++	+
Tension-Anxiety	++	++	+	++	++	0
Anger	+	0	0	0	0	0
Depression	+	+	0	+	+	−
Fatigue-Inertia	++	0	+	0	++	−
Vigor	++	+	0	0	+	0
Confusion	0	0	++	+	0	+

++ = Significant improvement.
+ = Improvement trend, short of significance.
0 = No or slight change.
− = Worsening trend, short of significance.

TABLE 8. SUMMARY OF PRE-POST CHANGES (*t* TESTS) ON THERAPIST CRITERIA

	Group		
	Li and Ptx	Pl and Ptx	Ptx Only
Status Ratings			
Hostile Belligerence	0	0	0
Anxious Intropunitiveness	++	++	0
Manifest Tension	+	0	+
Severity of Illness	++	0	0
Interview Relationship			
Rapport	++	+	+
Blocking-Silence	0	0	0
Antagonistic-Resistive	0	0	0
Leading-Controlling	0	0	0
Ingratiating	0	0	−

++ = Significant improvement.
+ = Improvement trend, short of significance.
0 = No or slight change.
− = Worsening trend, short of significance.

a tendency to get worse. The Psychotherapy Only Group showed a reduction in Somatic and Psychic Discomfort, in Tension-Anxiety, and in Fatigue. Also of interest was that the Placebo Only patients showed a pattern of changes similar to the Psychotherapy Only Group. Over the short run of the study, giving a patient a capsule apparently helps.

Results of tests of pre-post changes in therapist criteria are given in Table 8. It will be observed that in the capsule groups, Anxious Intropunitiveness was significantly reduced. Also, Rapport was significantly increased and severity of illness rated as significantly reduced in the drug group. The results again support the notion that the drug does have distinct effects, but also that the giving of capsules in itself can reduce anxiety. However, therapists for the Psychotherapy Only patients did not observe less anxiety, although patients reported less after four weeks.

Interview relationships

Another question asked at the beginning of the study was whether chlordiazepoxide facilitated or impeded the interview relationship. Six measures were included, of which five are in Table 5. It is evident that the drug did not impede the interview relationship as assessed here. On the contrary, it tended to improve interview rapport. At the close of the study, each therapist was asked to judge the effect of medication on psychotherapy. Did it facilitate therapy, impede the process, or do both, or neither? Therapists judged medication for 32 per cent of the 50 cases involved to be facilitating; for 64 per cent of the patients, medication was neither impeding nor facilitating.

In this connection it is interesting to note that the therapists did guess better than chance who received placebo and who received the active drug. Their guesses were 64 per cent correct.

DISCUSSION

The initial study reported by the authors concerned two drugs: meprobamate and chlorpromazine.[6] The investigation was designed to determine whether the two tranquilizers used as adjuncts to individual psychotherapy were more effective in reducing anxiety and hostility than psychotherapy with phenobarbital, psychotherapy with placebo, or psychotherapy alone. Patient measures taken before and after eight weeks of treatment indicated that neither tranquilizer, used adjunctively, had an advantage over either control substance or over psychotherapy alone in reducing anxiety or hostility. Similarly, from the viewpoint of the therapist, anxiety was reduced about equally in the five treatment groups.

A careful consideration of the above findings suggested that the drugs may have had an appreciable early effect which was wiped out over the eight-week period by various factors of adaptation, or that other treatment groups overtook the drug groups by the close of eight weeks. Further, a study of the pattern of medication effects over time seemed to be needed. It was to solve some of these problems that the present study was designed. Clearly, while a different drug was used, the findings of the present experiment do tend to support the hypothesis that there may have been distinctive early drug effects which were no longer evident after eight weeks of treatment. The study also indicates that the pattern of effects for Drug, Placebo, Psychotherapy Only, and Wait Groups over time are quite distinctive and deserve further evaluation in future studies.

VOL.
1
1962/

How influential is psychotherapy in this context? First, it should be noted that the experiment was not intended to evaluate psychotherapy *per se*, only its short-term influence on anxiety and its interactive effect with the drug. Does it potentiate, moderate, or nullify the influence of the drug, or none of these? In part, the answer depends on whom you ask, the patient or the therapist. In the first study, Psychotherapy Only patients did as well as patients receiving drugs or placebos over the eight-week period. The answer was consistent across patients and therapists. In the four-week study, patients receiving psychotherapy on the average did no better than those not receiving psychotherapy. But it is important to note that the Wait Group did not improve at all, while the improvement reported by Psychotherapy Only patients was significant and in a pattern very similar to the group also receiving the drug. From the viewpoint of the therapist, addition of the drug reduced Anxious Intropunitiveness, Severity of Illness, and increased Rapport (Table 8). The Psychotherapy Only patients did not exhibit this pattern.

In what way if any, can the known pharmacological properties of chlordiazepoxide account for the present findings? RANDALL[7] has described some of the drug's pharmacological actions. It has unique taming effects on monkeys below the ataxic dose. It is a muscle-relaxant in monkeys, dogs, cats and rodents. In mice the drug is a potent anticonvulsant. Unlike chlorpromazine it does not produce autonomic blocking. It also lacks hypnotic effects at high doses. The drug has appetite-stimulating effects on rats and dogs. The reported effects of muscle-relaxation, taming and appetite stimulation are consistent with the findings reported here of early reduction in tension-anxiety, the heightened sense of well-being (Vigor score), and improved rapport with others.

The results reported here are also consistent, for the most part, with clinical and controlled reports.[8–10] The major novel finding is the extent to which anxiety can be reduced simply by giving a patient a capsule.

SUMMARY

A four-week double-blind study was made of the effects of chlordiazepoxide on a group of 150 male outpatients newly accepted for individual psychotherapy. Three major hypotheses were tested. The findings with respect to patient criteria were:

1. patients receiving the drug reported themselves no better than placebo patients with but one exception;

2. patients receiving either capsule (chlordiazepoxide or placebo) reported a greater reduction in tension, anxiety and depression, greater over-all improvement, and more social changes than patients not receiving capsules;

3. treatment groups receiving psychotherapy combined with drug or placebo reported themselves no differently from patients not receiving psychotherapy (except for the Wait Group).

The findings for patients receiving psychotherapy as reported by their therapists were:

1. patients receiving the drug were significantly less severely ill, in better rapport with others, and better able to express affection;

2. groups receiving either the drug or a placebo as compared to the group receiving

only psychotherapy showed significantly greater reduction in anxiety, self blame, physical complaints, and greater over-all improvement.

From the standpoint of patient self reports, only after the first week did patients receiving the drug show greater changes than those receiving placebos. They reported less tension-anxiety, greater vigor and more over-all improvement. These effects wash out by the end of four weeks. After four weeks placebo patients report as much change as chlordiazepoxide patients.

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VOL.
1
1962/

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A FURTHER STUDY ON ALLEVIATION OF THE PSYCHOLOGICAL EFFECTS OF LSD IN MAN BY PRETREATMENT WITH 5-HYDROXYTRYPTOPHAN

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DL.
1
62/63

ON THE basis of the peripheral antagonism between lysergic acid diethylamide (LSD) and serotonin on smooth muscle, the concept arose that a similar central antagonism might account for the psychotomimetic properties of LSD.[1–3] Recently, BRENGELMANN *et al.*, [4] after studying the evidence for such a central antagonism, have obtained experimental evidence of their own which supported the hypothesis. These authors tested the hypothesis in man by using 5-hydroxytryptophan (5-HTP) in an effort to increase brain concentrations of serotonin. As predicted, the effects of LSD when preceded by 5-HTP were less than those following a similar injection preceded by saline. However, the moderating effects of 5-HTP were apparent only in the results of psychometric tests; with the dosage of 5-HTP used (25 mg), the after effects of the two LSD injections could not be distinguished on clinical observation. Only five subjects were used.

The present investigation was designed to repeat these experiments using higher doses of 5-HTP hoping that a clinically apparent alleviation of the LSD symptoms might be obtained.

METHOD

Drugs and dosage

In preliminary experiments, intravenous 5-HTP (DL) was given daily in increasing dosage to establish the maximum dose for each individual (Table 1). The occurrence of side effects was accepted provided these had completely subsided within 45 min after the injection of 5-HTP, or 15 min prior to the injection of LSD.

Similar experiments were done to establish the intravenous dose of LSD which would produce symptoms which could be quantified clinically, would leave the subject co-operative, able to carry out psychological tests, and willing to repeat the experience on subsequent occasions (see Table 1). The dose of LSD was considered adequate when it produced mild, but definite, perceptual disorders, in addition to the changes of mood which frequently occurred at lower dosages. These perceptual disorders were much more easily quantifiable than the changes of mood for assessing differences between experiments. These preliminary

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TABLE 1. RATING SCALE SCORES AFTER PRETREATMENT WITH 5-HYDROXYTRYPTOPHAN (5-HTP) AND SALINE AND AFTER INTRAVENOUS LYSERGIC ACID DIETHYLAMIDE

Subject No.	5-HTP Dosage	After Saline or 5-HTP: 0		½ hr		1 hr		LSD Dosage	Time after LSD Injection: ½ hr		1 hr		2 hr		3½ hr	
		S[1]	H[2]	S[1]	H[2]	S[1]	H[2]		S[1]	H[2]	S[1]	H[2]	S[1]	H[2]	S[1]	H[2]
1*	40 mg	5	3	4	17			40 μg	29	13						
2*	25 mg	2	2	3	13			30 μg	20	19						
3*	40 mg	4	5	4	7		6	50 μg	5	7	12	7	38	11	40	9
4*	40 mg	0	1	0	5	0		50 μg	14	5	21	5	61	18	21	6
5	35 mg	3	4	4	10	4	4	40 μg	21	15	25	35	17	57	12	18
6*	45 mg	3	3	3	7	3	3	50 μg	52	40	60	57	74	58	62	44
7	35 mg	3	3	3	9	3	3	40 μg	29	28	45	37	36	21	30	28
8	30 mg	0	2	2	3	1	5	40 μg	10	17	16	37	42	21	13	28
9*	45 mg	1	2	5	7	4	4	50 μg	42	26	44	30	36	25	23	16
10	60 mg	3	3	1	5	2	4	60 μg	27	29	55	55	68	66	71	73
11*	60 mg	2	1	1	1	2	2	60 μg	40	19	58	30	46	37	38	19
12*	55 mg	0	0	1	2	0	6	50 μg	16	4	18	10	22	12	17	9
13*	55 mg	3	1	1	6	2	0	55 μg	46	27	94	72	62	74	61	50
Mean ± S.D.																
Saline Pretreatment:		2 ± 2		2 ± 2		2 ± 2			27 ± 15†		41 ± 25		46 ± 19		35 ± 21	
5-HTP Pretreatment:		2 ± 1		7 ± 4		3 ± 2			19 ± 11		34 ± 21		36 ± 23		27 ± 20	

[1] Rating Scale scores obtained at the designated periods when saline was the pretreatment.
[2] Rating Scale scores obtained at the designated periods when 5-hydroxytryptophan was the pretreatment.
* In these subjects the clinical prediction of the date of 5-HTP administration was correct.
† This difference is statistically significant at $P<0.02$.

VOL. 1 1962

experiments, by affording the subjects an LSD experience and familiarizing them with the psychological tests (see below), allowed subsequent experiments to be more comparable. To avoid tolerance effects, these preliminary studies were always done at least one week before the experiment proper.

Subjects

Seventeen healthy volunteers between the ages of 18–25 years, were given a rigorous physical and psychiatric examination prior to the experiment. Of these, four had to be rejected because they developed gastrointestinal symptoms at a low dosage of 5-HTP. Of the remaining 13 subjects, 9 were female.

Design

After preliminary experiments to establish optimal doses of 5-HTP and LSD, each subject was given an intravenous injection of saline or of 5-HTP, followed in one hour by an intravenous injection of LSD. One week later, at the same time of the day, the subject was given an intravenous injection of the alternative pretreatment followed in one hour by LSD. The order of saline or 5-HTP injection on the first week was randomized for each individual by the toss of a coin. In the case of 8 subjects the order of injections was saline preceding the LSD on the first occasion, and in the case of 5 subjects the 5-HTP was given on the first occasion. Neither the subjects nor the assessing investigator were informed as to the occasion on which 5-HTP was administered. Several times the occurrence of nausea and vomiting served as strong clues to the subjects as to when they had received 5-HTP, but the accuracy of these guesses by the subject was not made known to them during the study. Both the subjects and the assessing investigator were informed that LSD was given at each experimental period.

Assessment of symptoms

The assessor was admitted to the test room just prior to the injection of LSD and only when side effects, if any, of 5-HTP had completely subsided. Assessment of symptoms was made in three ways: 1, Clinically, i.e. by interview and behavioral observation; 2, by a four point rating scale[5] previously shown to be a valid test of LSD symptoms, [6] and 3, by a self-administered mood scale.[7] The assessment was carried out at one-half, one, two, and three and one-half hours after the LSD injection. When the experiment on each individual was completed, and before scoring the rating scale, the assessor made a clinical judgement as to which week the subject had been given 5-HTP. The mood scale was scored mechanically using the IBM 650 computer.[8]

RESULTS

1. 5-HTP regularly resulted in mild gastrointestinal symptoms and occasionally a slight fall of blood pressure. In no case did these symptoms persist from more than 20–30 min and in every case the symptoms had subsided 15 min prior to the LSD injection. In addition to these frequently described side effects, one patient repeatedly felt drowsy and yawned following 5-HTP administration.

In Table 1 the scores for the Symptom Rating Scale are shown; the more marked the

symptoms, the higher the score. During the one hour period after the initial injection, but before LSD, it can be seen that the mean scores are significantly lower than after LSD and it is particularly of interest that there is no significant difference between the mean scores after the saline and 5-HTP pretreatments at the period just prior to LSD administration (saline = 2·1 ±1·5, 5-HTP = 3·1 ±2·0; mean ± S.D.).

2. Effect of 5-HTP on LSD. Acting on the assumption that 5-HTP reduces LSD symptoms, the assessor was required to make a definite prediction in each case, as to the occasion on which 5-HTP had been given. He was correct in the case of 9 subjects and wrong in four (Table 1); the accuracy of this clinical assessment is not statistically significant.

The mean results on the rating scale showed fewer LSD symptoms on the occasions when the subjects were pretreated with 5-HTP, as compared to saline pretreatment, at each of the test periods. For eleven subjects, numbers 3 through 13 (Table 1) the test data are relatively complete; 6 of these subjects received saline on the first occasion and 5 subjects received 5-HTP on the first occasion. When analyzed statistically using a cross-over design, no order effect was found at any of the test periods. However, the drug effect, i.e. pretreatment effect as measured by this rating scale, was statistically significant at the ½ hr test period ($F = 2{\cdot}83$, $p<0{\cdot}02$), but not statistically significant at the later time periods. The rating scale scores at ¼, 1, 2, and 3½ hr after LSD for the occasions when 5-HTP was the pretreatment was subtracted from the scores for the corresponding periods for the occasions when saline was the pretreatment. These differences in the scores were found to be significantly correlated ($P = 0{\cdot}05$) with the dose of 5-HTP at the ½ hr test period ($r = +0{\cdot}58$) and at the 1 hr test period ($r = +0{\cdot}62$).

Although the mood scale showed a distinct change after LSD, it revealed no difference between the occasions when 5-HTP was given and when saline was given as the pretreatment (Table 2).

DISCUSSION

KLEE *et al.*[9] also have attempted to alleviate the psychological effects of LSD with 5-HTP but found no effect. Following the administration of 5-HTP by slow intravenous drip, they gave the LSD orally and assessed the subjects' mental state three to five times on each experimental day and again the following day. Klee's negative findings might be explained by: 1, insufficient sensitivity and precision of the clinical evaluation, as found in our study, 2, low dose rate of the intravenous administration of 5-HTP (1·11 mg/min in the case of one subject; no details were given regarding the others), or 3, other difficulty in timing of the observations so that they did not correspond to the peak period of LSD effect.

In our study the 5-HTP was administered intravenously over about 10 sec; this method of administration can be expected to produce maximal gastrointestinal and other symptoms within 15 to 20 min followed by a decrease. In agreement with the report of DAVIDSON *et al.*,[10] we found that lengthening the period of infusion up to 30 min did not eliminate the gastrointestinal symptoms. Therefore, we used the 10 sec infusion period so that the gastrointestinal symptoms would be gone before the LSD was administered. The effect of 5-HTP or saline pretreatment on the symptoms arising after LSD is statistically significant ($P<0{\cdot}025$) only at the half-hour period after LSD. At this period the LSD symptoms are fewer and therefore the percentage difference is greater. In addition, the variance is much

VOL.
1
1962/

Table 2. Mean ratings* of factors from the Clyde mood scale on 11 normal subjects pretreated with 5-HTP or saline followed by LSD

C M S Factors	Pretreatment	Test Periods 1	2	3	4	5
Friendly	5-HTP	47·5	39·3	38·8	36·9	35·5
	Saline	47·0	44·0	39·0	40·8	43·2
Energetic	5-HTP	49·8	41·0	38·1	39·0	37·6
	Saline	50·5	47·2	34·2	41·4	43·7
Clearthinking	5-HTP	51·1	47·6	37·1	35·1	36·8
	Saline	52·0	50·6	35·8	36·1	42·5
Aggressive	5-HTP	41·2	39·0	43·4	44·5	45·8
	Saline	41·8	40·5	42·5	47·4	46·5
Jittery	5-HTP	44·9	44·1	56·4	59·2	57·6
	Saline	47·3	43·4	59·1	61·8	55·0
Depressed	5-HTP	40·1	42·3	45·8	49·0	48·8
	Saline	40·6	41·6	47·4	47·7	46·5

* The data in this table are standard scores (5a). The test period 1 preceded any treatment, test 2 was administered 1½ hr after saline or 5-hydroxytryptophan (5-HTP) injection and periods 3, 4 and 5 were 1½ hr, 2 hr, and 3½ hr after LSD injection.

less, the smaller variance ($S^2 = 323$) is the factor which makes the difference of 7·9 statistically significant at the half-hour period while the larger difference of 9·2 at the two hour period is not statistically significant because of the larger variance ($S^2 = 881$) of the scores at this period.

Udenfriend *et al.*[11] have reported on the changes in serotonin content of rat brains following iproniazid (75 mg/kg) and 5-hydroxytryptophan (100 mg/kg). In contrast to their findings, we would expect smaller elevations of serotonin in brain, and an earlier onset of decline, in view of the instantaneous administration and much lower doses (0·4 to 0·9 mg/kg) used on the subjects in our study. On the basis of these considerations, the brain levels of serotonin would be expected to be decreasing during the later test periods after LSD; this suggests an explanation as to why pretreatment does not show a statistically significant influence on the LSD effect at the later periods.

The present investigation closely followed the methods used by Brengelmann *et al.*[4] and the results are in agreement, i.e. the results of the symptoms rating scale were more reliable than clinical assessment in evaluating the pretreatment effect of 5-HTP on the symptoms produced by LSD.

The finding of a statistically significant correlation between the 5-HTP dose and the difference between the scores ("5-HTP pretreatment" minus "saline pretreatment") on the rating scale at the ½ and 1 hr periods, also lends support to the hypothesis that 5-HTP pretreatment lessens the effect of LSD. In addition, the accuracy of the clinical assessment is related to dose; at 40 mg of 5-HTP there were 8 correct assessments out of 9 trials; while at less than 40 mg only one was correct out of 4.

In contrast to the findings with the Symptom Rating Scale, the Clyde Mood Scale, though demonstrating a response to LSD, revealed no significant differences between the occasions when LSD was preceded by 5-HTP or saline. A possible explanation for the discrepancy between these two psychological tests may be that the Symptom Rating Scale is more specific for drug effects while the Clyde Mood Scale measures more general changes in affect.

The results obtained by BRENGELMANN *et al.*[4] and in this study in which 5-HTP pretreatment appears to lessen the effect of LSD, may be explained at least two ways. First, these results may suggest a direct antagonism between 5-HTP (or its product, serotonin), and LSD in the brain; this explanation has been advanced earlier by others, as mentioned above.[1–4] Secondly, it is well known that sedatives such as sodium amytal lessen the psychological effects of LSD. Although such a sedative action was not discernible in Brengelmann's tests, one of our subjects repeatedly became drowsy and yawned following 5-HTP. Such a nonspecific effect of 5-HTP on LSD cannot be excluded.

In conclusion, the results of this study provided further evidence that 5-hydroxytryptophan pretreatment reduces LSD symptoms in man, which it may do by increasing brain serotonin. This finding lends further support to the hypothesis that LSD produces psychotomimetic effects in man by a central antagonism to serotonin.

VOL.
1
1962/

SUMMARY

In this study of the possible alleviation of LSD symptoms by pretreatment with 5-hydroxytryptophan (5-HTP), the dose of 5-HTP was increased to a maximum under the experimental conditions. Nine female and four male subjects were given an intravenous injection of 25 to 60 mg of DL-5-HTP or 0·9 per cent saline solution followed, in one hour, by 30 to 60μg of lysergic acid diethylamide (LSD). The pretreatment was given in a double-blind design. Clinical assessment of the occasion on which 5-HTP was the pretreatment was correct in 9 cases (not statistically significant). The Symptoms Rating Scale was administered before, $\frac{1}{2}$ hr, and 1 hr after the pretreatment, and $\frac{1}{2}$, 1, 2, and $3\frac{1}{2}$ hr after LSD. The results obtained on this scale showed significantly ($P<0{\cdot}02$) fewer symptoms $\frac{1}{2}$ hr after LSD on the occasion when 5-HTP was the pretreatment. The results on the Clyde Mood Scale showed an LSD effect, but no significant effect of pretreatment.

The findings of this study are in agreement with an earlier study and strengthen the conclusion that pretreatment with 5-hydroxytryptophan decreases the symptoms produced by lysergic acid diethylamide. The mechanism of this action is not yet clear; it may possibly be due to an increase of serotonin in the brain as a result of the administration of its precursor, 5-hydroxytryptophan.

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OL.
1
62/63

VOL.
1
1962/

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THE RELATIONSHIP BETWEEN LEVEL OF SKIN POTENTIAL AND FUSION OF PAIRED LIGHT FLASHES IN SCHIZOPHRENIC AND NORMAL SUBJECTS

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OL.
1
62/63

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A STUDY reported by LINDSLEY[1] presented evidence to show that the representation of paired light flashes in the optic cortex is modified by stimulation of the reticular system. As a result of the discussions of physiological data presented by LINDSLEY,[2] HEBB,[3] and MALMO,[4] findings on the activity of the reticular system have become associated with previous psychological ideas such as "energy mobilization"[5] under the general heading of arousal.

The present study was carried out to determine whether there was any relationship between the subjective report of threshold of fusion of paired light flashes, which on the basis of LINDSLEY's study might be expected to have some relationship to reticular activity, and level of skin potential. This latter variable was chosen[6] as a parallel to level of skin conductance because its measurement was thought to have certain electrical advantages over skin conductance. Skin conductance was a measure which had been frequently used, for example by FREEMAN[7] as an index of arousal or its conceptual forerunners.

METHOD

Apparatus

(1) *Skin potential measurement.* Full details of the technique are given elsewhere.[6] Skin potential was measured by means of a D.C. amplifier with an input impedance of 5 MΩ. A decade backing off circuit in the input enabled skin potential levels between 0–100 mV to be compensated for in steps of 1 mV so that the centre point on a paper record corresponded to the backing off voltage. The subject's potential was then measured from this point. The output of the amplifier was fed to a recorder providing a continuous trace capable of being read to the nearest 0·1 mV. The drift of the amplifier after warming up was less than $\pm 20\mu$V in 30 min. The average testing session took 20 min. Silver — silver chloride electrodes were used, pairs were selected to have less than $\pm 100\mu$V standing potential in

0·5 gm/100 ml potassium chloride solution. The measured drift of a sample of electrodes was less than 50μV in 20 min. The electrode jelly which was used, consisted of a 0·5 gm/100 ml solution of potassium chloride made up with 2·0 gm/100 ml agar-agar. The amplifier was used in an unbalanced condition; a single earth electrode was placed over a point on the inner surface of the forearm at about seven to eight inches from the wrist. This point was thoroughly scarified with fine sandpaper to achieve a zero potential point and a source resistance of 100 KΩ or less. The active electrode was placed on the hypothenar eminence. The skin at this site was unprepared except for cleaning with ether.

The temperature of the experimental room was maintained at between 19 and 21°C. The potential artefact arising from the use of non-isothermal electrodes was compensated for as described in.[6]

(2) *Two flash threshold measurement.* The apparatus for producing paired light flashes used as its light source the Ferranti CL.66 cathode ray tube. This tube has a phosphor which results in an essentially white source of light. The maximum luminous area is approximately 5 cm in diameter. Pulses applied to the grid of the tube resulted in square wave pulses of light. The decay time of the tube phosphor is approximately 5μsec.

Associated timing equipment made possible the presentation of two flashes of light whose durations were independently variable from 1 to 30 msecs. The interflash interval was capable of being continuously varied between 1 and 700 msecs. In the working range of the experiments between 30 and 140 msecs, the interflash interval could be set to the nearest msec. Neutral density filters placed in front of the tube face made it possible to attenuate the intensity of the flashes from a maximum of 5000 ft L. Masks with circular holes placed in front of the neutral density filters served as a means of varying the visual angle.

Preliminary experiments were carried out to determine what were best working parameters of intensity, flash length and visual angle. No effect on threshold of variation of visual angle over the range 0·48° to 1·90° was found. Between 50 ft L and 2000 ft L no effect of intensity was evident. Flashes of 5000 ft L produced higher two flash thresholds than those to intensities in the 50–2000 ft L range. Thresholds were found to vary inversely with flash lengths between 5 and 20 msec. On the basis of these results and subjective reports of ease of carrying out the task the following parameters were finally adopted. Intensity 50 ft L, visual angle 1·8°, flash length 5 msec.

A fixation patch was provided by edge illumination of a perspex block placed in front of the tube face. The intensity of the patch was 0·025 ft L.

Two matt black screens 3 ft square with square knife-edge holes of side 5 in. and 8 in. were placed 8 in. and 11 in. in front of the tube face. These served to prevent stray light from reaching the subject's eye.

The experimental room was completely darkened.

Procedure

The subject was seated with his eyes approximately four feet from the tube face, which he viewed binocularly. He was asked to rest his head between two pads on the chair back which kept it in line with the optical axis of the apparatus. He was told he would see either one or two flashes of light and that all he had to do was to report the number by giving one

VOL. 1 1962/

or two presses on a button conveniently situated at his right hand. Preliminary practice was given until the subject felt confident that he could do what was required.

The electrodes for the measurement of skin potential were placed in position and the subject was asked to sit for three minutes so that his eyes would become accustomed to the dim light from the fixation patch. At the end of this period he was told through a loudspeaker that the experiment would start.

If the two flash threshold can be thought of as a measure which is affected by the state of activity of the brain stem reticular formation it is to be considered likely that it will be subject to alternations over time as reticular activity changes. It is not possible to estimate what time course these variabilities might have. However, it is possible that while spending some 15 to 20 min in obtaining a threshold by, for instance, the full constant method, the physiological determinant of the threshold might itself change and render the measure invalid. A short method of measurement of threshold was therefore indicated. That which was used here, a modification of the constant method, enabled a threshold to be determined in about 1½ to 2 min, which was important not only for the reasons given above but also because it allowed results to be obtained from fairly disturbed schizophrenics whose attention could not be kept for a longer period. These subjects tended to give random results if the threshold could not be obtained within about 20 presentations.

The threshold of fusion of the two light flashes was determined by the following technique. A pair of flashes with a long interflash interval say 100 msec was presented. If the subject then pressed twice, flashes with a short interflash interval were presented. If the subject then pressed once, the procedure was repeated with decreasing range until two interflash intervals a millisecond apart at which the subject reported with two presses to the longer and one to the shorter were reached. Pairs of flashes with these interflash intervals were then twice repeated and if the responses were maintained the last interflash interval at which the subject pressed once was taken as the threshold. The skin potential just before this final pair of flashes was noted. The following sequence is from a typical record.

100–2	50–1	90–2	60–1	70–1	80–2	70–1	75–1	78–2
77–2	75–1	76–1	76–2	75–1	75–1	76–2	$75\text{–}1^{P}$	76–2

P = Potential taken at this point.

Because it was thought that this short method of obtaining a threshold might be unreliable an experiment was carried out to determine the reliability of two thresholds taken 4 min apart. Fifty schizophrenics and twenty-five normal subjects were tested. While bearing in mind the circular arguments involved the ongoing state of the subject was monitored by his skin potential level. Only those subjects whose skin potentials on the two occasions were within the arbitrarily selected figure of 3 mV were used for reliability measurement. It was found that for the 38 schizophrenics and 20 normals whose potentials remained within these limits and whose thresholds on either occasion were less than 140 msec, the correlation between the thresholds taken on the two occasions was 0·96. Six patients whose thresholds were greater than 140 msec on one occasion tended to give very different thresholds on the other occasion. It was therefore decided in future to discard the data of patients with thresholds greater than this figure.

Correlations of threshold with age were +0·17 for the normals and +0·05 for the schizophrenics. Neither correlation is significant.

Although recorded continuously the measurement of potential was taken at a single point as shown above. It was found that after initially giving responses to the presentation of the flashes, most subjects' records showed marked adaptation. The potential measurement at the final flash presentation usually took place on a relatively invariant stretch of record. Where any responses were present the level about which they took place was the potential which was used.

Subjects

All schizophrenic subjects tested had been in hospital for longer than two years, and could therefore be considered chronic. They ranged in age from 20–60 years. None of the patients was under sedation or was currently receiving, or had recently received tranquillizing drugs. None was lobotomized. There was definite evidence for all patients that they had had delusions, schizophrenic thought disorder or catatonic motor disturbances, at some time during their illness. All patients were interviewed by a psychiatrist* who rated them according to a sub-classification described in.[8] This classification enabled, among other things, the patients to be described for the purposes of the present study as non-paranoid or paranoid. Only those patients who were rated as having a high level of coherent delusions and relative lack of the other rated symptoms of flatness of affect, poverty of speech, and incoherence of speech were called paranoid. The remainder were classed as non-paranoid. No patients had histories of epilepsy or organic cerebral disease.

Normal subjects were drawn from the nursing, medical, and artisan staffs of the hospital in which the study was carried out.

RESULTS

Experiment 1

Thirty male non-paranoid schizophrenics took part. Their mean age was 42·5 SD 9·7 years and they had been in hospital for a mean stay of 8·0 SD 6·6 years. Three of the thirty patients gave thresholds in excess of 140 msec. These were considered likely to be unreliable and were therefore discarded. The mean threshold given by the remainder of the patients was 70·9 SD 13·5 msec, with a range of from 44 to 100 msec. The mean potential level observed was 27·9 SD 9·6 mV with a range of −10·5 to −42·5 mV. The sign indicates negativity at the hand, the active electrode.

The correlation between threshold and potential was calculated and found to be $-\cdot 79$, $P<\cdot 001$, $N = 27$. The relationship between the two variables could be represented by the regression line:

$$Th = -1\cdot 12P + 102\cdot 4 \text{ msec.}$$

The standard error of estimate of threshold from potential was 8·1 msec.

Experiment 2

As Experiment 1 showed a close relationship between two flash threshold and skin potential, but on a limited group of subjects, Experiment 2 was carried out to determine

* I am grateful to my colleague, Dr. J. K. Wing, for selection of the patients.

VOL. 1 1962/

whether the results would hold when using subjects of both sexes, normals as well as schizophrenics and including coherent paranoids among the latter group.

The ages and lengths of stay of the various groups are given in Table 1. Also shown are the numbers of subjects in each group having thresholds over 140 msec which were therefore considered as unreliable.

Table 1. Ages and length of stay in hospital of the subjects in experiment 2

Group	Normal		Non-paranoid Schizophrenic		Paranoid Schizophrenic	
Sex	M	F	M	F	M	F
No. tested	13	17	20	15	9	3
No. with unreliable thresholds	2	1	3	5	0	0
Age (years)	36·9 SD 9·9	35·1 SD 5·4	42·0 SD 9·3	40·5 SD 10·1	43·8 SD 7·8	43·3 SD 8·9
Stay (years)	—	—	12·2 SD 6·3	9·8 SD 5·2	11·3 SD 10·1	8·0 SD 3·5

For the normal subjects male and female combined the mean two flash threshold was 69·3, SD 12·9 msec with a range from 48 to 102 msec. Their mean potential was −29·8 SD 8·6 mV with a range from −8·5 to −43·0 mV. The correlation between two flash threshold and potential was found to be +·45, $p<·02$, $N = 27$. A slight suggestion of curvilinearity in the plotted data was tested and found to be non-significant. The linear regression between two flash threshold and skin potential was

$$Th = +0{\cdot}65\,P + 50{\cdot}0 \text{ msec}$$

The standard error of estimate of threshold from potential was 11·1 msec.

The non-paranoid schizophrenics, male and female combined, gave a mean two flash threshold of 72·1, SD 15·9, with a range from 52 to 96 msec. Skin potentials ranged from −12·0 to −58·0 mV with a mean at −31·3, SD 12·0 mV.

The correlation between two flash threshold and skin potential for this group was −·72, $p<·001$, $N = 27$. The regression line relating threshold to potential was

$$Th = -{\cdot}96\,P + 102{\cdot}3 \text{ msec}$$

The standard error of estimate of threshold from potential was 10·8 msec.

None of the data presented for this group differ significantly from that given by the similar diagnostic group of Experiment 1. Seven of the male schizophrenics were common to both experiments.

Only twelve coherently deluded paranoid schizophrenic patients satisfying all the other criteria mentioned above could be found in the hospital and could also be persuaded to take part in the experiment.

The mean threshold given by these patients was 70·3, SD 10·5 msec, range 56 to 95 msec, the mean potential was −33·8, SD 13·6 mV, range −12·8 to −55·8 mV.

The correlation between two flash threshold and skin potential was +·52 which was not significant for a group comprising only 12 subjects.

For comparison with other data the regression line relating two flash threshold and skin potential was calculated. Neither the slope nor the intercept values of the line $Th = +\cdot 40P + 56\cdot 8$ msec differed significantly from that given by the normal subjects. The standard error of estimate of threshold from potential was 8·9 msec.

In order to complete the examination of these data an analysis of variance was carried out to make a factorial comparison of regression lines from the categories: normal–non-paranoid schizophrenic, male–female. Ten subjects were selected at random from each category so as to obtain equal numbers in each group. Data from the paranoid schizophrenics were omitted because of the small numbers available.

The analysis produced a highly significant term concerned with the comparison of regression lines due to normal and schizophrenic subjects ($F = 51\cdot 09$, $p < \cdot 001$, df 1/36) but those terms due to sex and the interaction between sex and diagnosis were not significant. The data for all groups in this experiment are shown graphically in Fig. 1.

VOL.
1
1962/

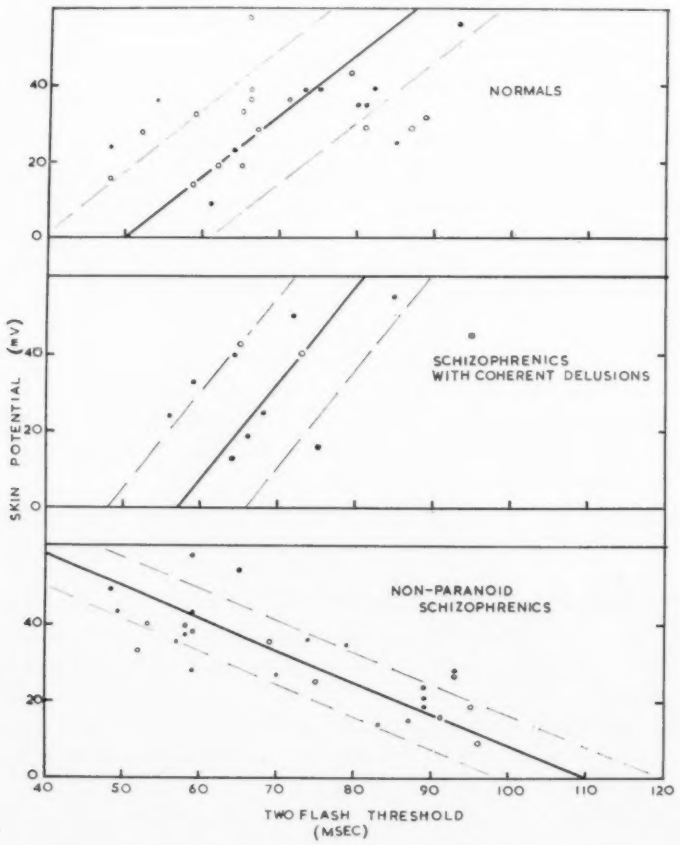

FIG. 1. Regression lines relating two flash threshold and skin potential for normal, deluded schizophrenic and non-paranoid schizophrenic groups in Experiment 2. Filled circles male subjects, open circles female subjects.

Experiment 3

As the results of Experiment 1 on non-paranoid schizophrenics had been confirmed in Experiment 2 and the relation between two flash threshold and skin potential in normals had been shown to be the opposite of that in schizophrenics it was decided that confirmation of this result with a second normal group was required.

Twenty-five normal subjects of mean age 34·6, SD 9·7, range 23–56 years were tested. Fifteen were men and ten were women. The mean of their two flash threshold was 69·5, SD 12·5 msec, with a range from 48 to 93 msec. Their mean potential was −31·2, SD 10·4 mV ranging from −14·0 to −57·6 mV.

The correlation between threshold and skin potential was +·61, $p<·001$, $N = 25$, and the regression line relating threshold and potential $Th = +·73\,P + 46·8$ msec. The standard error of estimate of threshold from potential was 7·8 msec. The parameters of this regression line did not differ significantly from that obtained for the normal subjects in Experiment 2.

OL.
1
62/63

DISCUSSION

The experiments which have been described, provided replicated results to show that in chronic non-paranoid schizophrenics the threshold of fusion of paired light flashes was negatively related to level of skin potential. In normal subjects on the other hand, the relationship between the two variables was in the opposite direction. A small group of coherently deluded paranoid schizophrenics behaved similarly to the normals. The results present problems which can only be incompletely resolved.

The available evidence concerning the peripheral determinants of skin potential level, for example,[9–13] suggest that in contrast to skin conductance level, it is mediated only to a minor extent by sweat gland activity and although a simple membrane mechanism does not adequately fit the facts[14] something approximating to a semi-permeable membrane is involved. If this is the case, variations in skin potential with an external electrolyte of fixed constitution may be due either to variations in the composition and concentration of electrolytes internal to the membrane or alternatively to alteration in the degree of permeability of the membrane itself. Insufficient direct evidence is available to suggest how either of these possible mechanisms might be controlled centrally.

The interpretation of the two flash threshold findings is similarly uncertain. Lindsley[1] clearly interprets reticular stimulation as having a facilitatory effect upon the ability of the cortex to resolve paired light flashes. Similar results are obtained in the auditory modality by Steriade and Demetrescu.[15] On the other hand Evarts *et al*[16] provide evidence to show that the cortical response to the second of a pair of shocks to the lateral geniculate body is depressed in the waking as contrasted to the sleeping animal.

Differences between these experiments, depending on whether they are carried out on intact or *encéphale isolé* animals, or whether stimulation is to the periphery or to sensory pathways makes it difficult to use these findings in interpretation of the present data.

The relationship between the appearance of cortical potentials and the perception of the

stimuli of which these potentials are the result has not been extensively studied. LINDSLEY[17] reports a study by himself and SCHWARTZ which tends to confirm, by means of conditioned responses to appearance of fusion and flicker, that response to these states parallel their cortical signs. STERIADE *et al*[18] report that in some subjects, following a loud noise which brought into operation the ascending activating system, there was a sensation that a repetitive photic stimulus was brighter and that this was related to an increase in the amplitude of cortical responses.

Bearing these difficulties of interpretation in mind, discussion of the diagnostic differences in results can be no more than speculation. JASPER[19] has suggested that the function of the reticular system in normal adaptive behaviour is a regulatory one and its function is to prevent indiscriminate arousal to all stimuli. He further suggests that lack of this regulation may be the feature of certain mental disorders.

Paraphrasing this suggestion as an interpretation of the present results suggests that in the non-paranoid schizophrenic autonomic and cortical arousal operate in parallel, cortical level being uncontrolled by the regulatory activity of the reticular system. However, it may be suggested that in the normal subject the regulatory activity of the reticular system tends to modify the cortical activity so that the tendency is for cortical and autonomic indices to move in opposite directions.

One means of testing this hypothesis is to examine concomitant changes in two flash thresholds and skin potential when the organism is subjected to an external disturbance such as a loud noise. The present results which are based upon inter-subject differences in skin potential and two flash threshold would then be extended by the examination of the relationship of changes in these indices within the subject.

VOL.
1
1962/

SUMMARY

Skin potential levels and thresholds of fusion of paired light flashes were measured in three experiments carried out on chronic schizophrenic and normal subjects. Thirty patients took part in the first experiment, 47 patients and 30 normal subjects in the second and 25 normal subjects in the third.

Replicated results showed negative relationships ($r = -0{\cdot}79$, $r = -0{\cdot}72$) between two flash threshold and skin potential in non-paranoid schizophrenics and positive relationships ($r = +0{\cdot}45$, $r = +0{\cdot}61$) in normal subjects. Coherent paranoid schizophrenics showed a similar pattern of results to those of normals ($r = +{\cdot}52$). The physiological basis for the results is discussed and a tentative interpretation proposed in terms of a cortical regulatory system present in normals which is relatively non-functional in non-paranoid schizophrenics.

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OL.
1
62/63

VOL.
1
1962/

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CLINICAL EXPERIENCE WITH DIHYDROXYPHENYLALANINE (DOPA) IN DEPRESSION* †

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OL.
1
62/63

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1. INTRODUCTION

THIS is a report of the results of a clinical trial of dihydroxyphenylalanine (DOPA), a precursor of catechol amines, in the treatment of depression. This experiment was undertaken as an indirect test of the *catechol amine theory of affective disorders*, which proposes that depressed patients have an absolute or relative deficiency of central nervous system (CNS) catechol amines, and that conversely, patients with elation have an excess of CNS catechol amines. The evidence in support of this theory derives from parallels between neuropharmacological investigations and clinical therapeutic experience with various psychopharmacologic agents, particularly reserpine and the MAO inhibitors.

Soon after they were found effective in excited and psychotic patients, including manic patients,[1] the Rauwolfia derivatives were discovered to alter CNS stored and free amines, particularly serotonin and norepinephrine. Reserpine, moreover, was found to induce severe depressive reactions in humans, especially hypertensive patients.[2] Based on these considerations, BRODIE *et al.* proposed that the clinical and pharmacological effects of the Rauwolfia derivatives were related to their capacity to alter brain amines.[3]

The therapeutic effectiveness of iproniazid, a monoamine oxidase inhibitor, in depressions further supported the idea that depressive states might be associated with a deficiency of

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CNS amines. Although the importance of the monoamine oxidase system in catechol amine degradation has required considerable modification following the demonstration of the catechol-O-methyl transferase pathway, therapeutic changes with MAO inhibitors are thought to be related to pharmacologically-induced increases in CNS amines.[4] The interactions between reserpine and various drugs, particularly MAO inhibitors and lysergic acid, received considerable attention, and, in many pharmaceutical laboratories, the effects of a new compound on the reserpinized animal were used as a screening test for possible anti-depressant actions. While there are many limitations to this model, the catechol amine depleted animal, expecially the reserpinized animal, provides a possible biochemical and behavioral analogue of some, if not all depressed states.[5]

Particularly relevant to the research reported here have been the experiments in which DOPA has been used to modify or reverse the effects of reserpine. DOPA has been investigated for a number of years because of its role in the synthesis of norepinephrine and other catechol amines.[6] Unlike norepinephrine, dopamine or serotonin, DOPA, when given parenterally in animals, will cross the blood-brain barrier and will contribute to increases in CNS amines. In animal studies, DOPA, but not 5-hydroxy-tryptophan, has also been shown to reverse both the behavioral effects and the depletion of CNS catechol amines that follows reserpine administration. These actions of DOPA are significantly potentiated by pretreatment of the animal with a monoamine oxidase inhibitor.[7–11] These experiments support the hypothesis that the catechol amines, rather than serotonin, are involved in the behavioral component of the reserpine depressed state.

The work cited above has been predominantly conducted in animals. Although a number of interesting and rationally consistent hypotheses relating behavior to brain amine metabolism were derived from these animal investigations, human studies with DOPA have been limited in number.[12–16] The few human experimentations undertaken have been in patients with cardiovascular diseases, schizophrenia, and, more recently, those with Parkinsonism and other extrapyramidal disorders.[17–19]

Based on the possible analogy between human depressed states and the amine-depleted animal, a clinical trial of DOPA alone and in combination with a MAO inhibitor in depressed patients was conducted to provide a partial test of the theory that CNS catechol amines are deficient in depressive states.

2. METHODS AND PROCEDURES

Clinical material

The patients in this study were female. Their median age was 52, with a range of 30–65 years of age. All patients showed moderate to severe depressive illness, manifested by sad affect, feelings of hopelessness, helplessness, worthlessness, and guilt. Other prominent clinical features were psychomotor retardation or agitation, early morning wakefulness, insomnia, anorexia, weight loss, loss of interest, anxiety, fatigue, or suicidal preoccupations.

Most of the patients have had protracted depressions prior to their admission. Less than half of the patients were referred to us within six months of the onset of their symptoms. Over half have been hospitalized previously for depressive episodes and many have received

VOL. 1 1962/

ECT. In summary, these patients represent a group of middle-aged women with recurrent severe depressions. Although the clinical features coincide with those usually regarded characteristic of "endogenous depressions", no assumption is made as to any specific etiological process.

Procedure

All studies took place on a special research ward at the Massachusetts Mental Health Center, where the research team has control over the selection of patients and their clinical care and treatment, including diet and medication.

On admission to the ward, patients were withdrawn from all psychopharmacological agents for at least one week, and thorough medical and psychiatric evaluations were undertaken. After this, they were placed on placebo for a minimum of one week, during which time, baseline biochemical and psychological procedures were conducted.

Patients were then allocated to treatment groups. They were randomly assigned on a single- or double-blind basis to treatment with placebo, imipramine (100–200 mg. daily), phenelzine (45–60 mg. daily), or D,L-DOPA (400–1200 mg. daily). Treatment was continued for a minimum of two to four weeks, at which time biochemical and psychological assessments were repeated. If a patient had not shown significant clinical improvement, the treatment was changed. A number of patients who had not improved on DOPA or MAO inhibitor were then treated with a combination of DOPA and phenelzine.

Assessment of clinical state

Changes in the patient's clinical state were assessed by two means:

(1) *Clinical Judgment of Improvement.* At the end of the course of treatment, while the identity of the medication was still unknown to them, the ward staff decided whether the patient's condition had sufficiently improved to warrant continuing with the study medication. If consensus was achieved that the patient was "improved", the trial was rated a "therapeutic success". If the patient was "unimproved", the trial was rated as a "therapeutic failure", and the patient's treatment was changed to another drug or ECT.

(2) *Ratings of Specific Psychopathology.* The contents of the daily ward observation notes were analyzed and ratings made of symptoms and behaviors in three categories:

(a) *Depressive Symptoms:* Fifteen possible items, including feelings of depression worthlessness, hopelessness or pessimism, of helplessness and of guilt; tearfulness, expressions of suicidal or death wishes; agitation, anxiety, or nervousness; difficulty in sleeping, fatigue, retardation, lethargy, and confusion.

(b) *Maladaptive Social Behavior:* Seven items, including eating problems; difficulty with ward or hospital routines; demanding or attention-seeking behavior; withdrawn; remaining in bed excessively; hostile, sarcastic, or angry comments; and appearance.

(c) *Report of Physical Complaints:* Records were also kept of patient's complaints, particularly cardiovascular symptoms, such as sweating, chills, dizziness, palpitations, or fainting; gastrointestinal symptoms; and other reports of bodily dysfunction.

Analysis of Data

The presence or absence of the above symptoms and behaviors was rated daily. Weekly scores within each of the three categories were obtained by summing daily ratings. Change scores were derived by the difference between the weekly ratings during the first and the last week of treatment with an individual agent. Two comparisons were made: (a) Change scores of the DOPA trials were compared with those of the placebo trials; and (b) Change scores of the DOPA-MAO inhibitor trials were compared with those of trials with MAO inhibitor alone. These comparisons were made by Fisher's *t* formula for testing a difference between uncorrelated means and the *t* formula for a difference between correlated pairs of means.[20]

VOL. 1 1962/

3. FINDINGS

Preliminary dose study

Preliminary experience was obtained with graded doses of oral D,L-DOPA. Doses up to 1200 mg. per day were non-toxic and easily tolerated. Above this dose, subjective effects of nausea and dizziness were reported. Very dark-colored urine was noted which was probably 3,4-dihydroxyphenylacetic acid.[13] From this experience 200 mg. of oral D,L-DOPA was established as the model dose to be administered three to six times daily.

Clinical trial of D,L-DOPA

As outlined in Table 1, seven female patients were treated with oral D,L-DOPA in doses ranging from 600–1000 mg. per day under single- or double-blind conditions for periods up to five weeks.

TABLE 1. CLINICAL DATA ON PATIENTS TREATED WITH ORAL D/L DOPA

Patient	Sex	Age	DOPA Treatment Maximum Dose	DOPA Treatment Duration	Clinical Outcome
M.W.	F	57	800 mg./day	15 days	Unimproved
J.C.	F	55	800 mg./day	23 days	Unimproved
H.S.	F	43	800 mg./day	23 days	Unimproved
B.S.	F	58	800 mg./day	24 days	Unimproved
C.S.	F	63	800 mg./day	32 days	Unimproved
P.M.	F	45	800 mg./day	72 days	Unimproved
M.V.	F	59	1200 mg./day	27 days	Unimproved

None of the patients was clinically judged to be improved sufficiently for the DOPA administration to be considered a therapeutic success. All were changed to other treatments, often with excellent results.

As shown in Table 2, there was no significant improvement in depressive symptoms,

social behavior, or physical complaints for patients during DOPA treatment trials ($N=8$) compared to placebo trials ($N=12$). There was a trend for aggravation of some aspects of psychopathology, but this did not reach statistical significance.

TABLE 2. EFFECTS OF DOPA TREATMENT ON SYMPTOMS, WARD BEHAVIOR, AND PHYSICAL COMPLAINTS OF DEPRESSED PATIENTS

Area of Psychopathology	Change Scores During Treatment* Placebo Mean	Placebo S.D.	DOPA Mean	DOPA S.D.	*t* Test	Significance Level
Depressive Symptoms	− ·81	5·77	+6·00	9·27	1·74	N.S.
Maladaptive Ward Behavior	−2·68	5·34	+1·25	4·84	1·61	N.S.
Physical Complaints	−1·33	2·96	+2·38	7·60	1·23	N.S.

* Scores are differences between weekly ratings before and after treatment.

No changes in blood pressure, pulse, temperature, liver function tests, blood count, or urine analyses were observed.

D,L-DOPA combined with MAO inhibitor

As outlined in Table 3, D,L-DOPA, 120–800 mg. daily, was administered in combination with phenelzine 45–60 mg. per day to five patients for periods of several days to five weeks. Of these five patients, three had failed to improve when previously treated with phenelzine alone, and two had failed to improve when previously treated with DOPA alone.

TABLE 3. CLINICAL DATA ON PATIENTS TREATED WITH DOPA-MAO INHIBITOR COMBINATION

Patient	Sex	Age	MAO Inhibitor Drug	MAO Inhibitor Maximum dose	DOPA Maximum dose	Duration	Clinical Outcome
E.K.	F	60	Phenelzine	45 mg./day	120 mg./day	8 days	Unimproved
M.V.	F	59	Phenelzine	45 mg./day	800 mg./day	8 days	Unimproved
E.C.	F	60	Phenelzine	60 mg./day	320 mg./day	13 days	Unimproved
B.S.	F	58	Phenelzine	45 mg./day	800 mg./day	27 days	Unimproved
P.M.	F	45	Phenelzine	60 mg./day	800 mg./day	91 days	Unimproved

None of the patients was judged improved. When their change scores were compared to trials of patients receiving MAO inhibitor alone ($N=14$), as shown in Table 4, no significant differences were found in any of the three categories rated.

TABLE 4. COMPARISON OF EFFECTS OF MAO INHIBITOR TREATMENT AND COMBINED MAO INHIBITOR-DOPA TREATMENT ON SYMPTOMS, WARD BEHAVIOR, AND PHYSICAL COMPLAINTS OF DEPRESSED PATIENTS

Area of Psychopathology	Change Scores During Treatment* MAOI Mean	MAOI S.D.	MAOI-DOPA Mean	MAOI-DOPA S.D.	*t* Test	Significance Level
Depressive Symptoms	−2·34	11·46	−4·16	6·98	·39	N.S.
Maladaptive Ward Behavior	+1·40	6·41	−2·00	6·99	·87	N.S.
Physical Complaints	+ ·31	5·79	+2·00	4·56	·61	N.S.

* Scores are differences between weekly ratings before and after treatment.

Cardiovascular effects of D,L-DOPA combined with MAO inhibitor

A transient elevation of blood pressure was observed in three patients of the five patients treated with D,L-DOPA combined with MAO inhibitor. This occurred with doses as low as 50 mg. of oral DOPA. Elevations of systolic blood pressure as high as 240 mm Hg have been observed, and there was also elevation of diastolic blood pressure as high as 150 mm Hg.

Subsequently, observations were made of additional patients receiving DOPA in combination with MAO inhibitor. These findings were confirmed.

During these hypertensive episodes, sinus bradycardia occurred. Some patients reported flushing, headache, palpitations, and uncomfortable feelings which were, in some respects, similar to anxiety attacks. These reactions are, in many ways, like those experienced by patients with actively secreting pheochromocytoma.

Biochemical determinations of plasma obtained at the peak of blood pressure elevation indicate increased level of catechol amines.[21] Bioassay methods confirmed elevation of pressor substance. Preliminary data suggest that norepinephrine may be the pressor amine involved. However, dopamine cannot be ruled out as the pressor substance until more complete analytical separations are conducted.[22]

VOL.
1
1962/

4. DISCUSSION

Earlier studies of autonomic dysfunction in psychiatric patients attempted to relate patterns of excretion of norepinephrine and epinephrine to psychological modes of reacting to stress.[23] More recently, attention has been focused on the possible role of various biogenic amines in the pathogenesis of psychiatric illnesses.[24, 25] In an early study from this research group, FRIEND observed euphoria in subjects receiving iproniazid in whom norepinephrine was infused. This mood elevation persisted for several hours, and suggested the possibility that, under the influence of MAO inhibitor, some norepinephrine had crossed the blood-brain barrier and had induced the euphoric response.[26] In further work, FRIEND observed that the metabolism of DOPA was altered in subjects receiving isocarboxazid (Marplan), a MAO inhibitor, or imipramine (Tofranil) in that compared to control conditions.

The peak of plasma catechol levels one hour after ingestion of 200 mg. D,L-DOPA was reduced in subjects receiving MAO inhibitor or imipramine.[12]

The possible therapeutic effects of DOPA in depressed patients were investigated because, in animal studies, it has been demonstrated that DOPA: (a) crosses the blood-brain barrier; (b) is involved in the synthesis of dopamine, norepinephrine, and epinephrine; and (c) will reverse the biochemical and behavioral effects of reserpine and other CNS amine depleting agents.

In this clinical trial, there were no indications that DOPA alone, or in combination with a MAO inhibitor, favorably influenced the clinical course of the depressive state. In attempting to understand the failure of this experiment to demonstrate that DOPA favorably influences depressive states, a number of possible factors, particularly dosage and the passage of DOPA into the central nervous system, need to be considered.

As regards dosage, it should be noted that the doses of DOPA used were considerably

lower than those used in animal studies. Determinations of plasma catechols by the WEIL-MALHERBE and BONE[21] method revealed marked rise in total plasma catechols within one to two hours after oral ingestion, with a return to normal levels by four hours. However, even with chronic administration of DOPA, or when DOPA was combined with MAO inhibitor, sustained elevations of plasma catechols were not observed. The elevations of blood pressure and associated symptoms, indicating the pharmacological effects of DOPA when combined with MAO inhibitor, were of short duration and probably are of peripheral origin. Even those patients exhibiting marked cardiovascular effects in whom plasma catechol amines were elevated, showed no subsequent changes in their clinical depression. Further increase of dosage is limited by the occurrence of hypertensive cardiovascular effects.

Although biochemical determinations showed transient elevations of plasma catechols following DOPA ingestion, there is not as yet, in the limited number of patients studied, evidence of a corresponding rise in spinal fluid catechols. Although spinal fluid catechol levels are somewhat elevated, the question remains whether DOPA, as administered in this study, passed the blood-brain barrier in sufficient amounts or at a rapid enough rate to exert the type of effect that has been seen in some animal experiments. It is quite possible that peripheral metabolic mechanisms act very rapidly to convert DOPA to dopamine and other substances and that only very small amounts of DOPA are available for transfer across the blood-brain barrier.[27, 28]

In this respect, it should be noted that actively secreting pheochromocytomas have few apparent actions on the central nervous system. Patients with such tumors do not experience euphoria, manifest excitement, or other indications of CNS effect. Furthermore, studies in our laboratory indicate that these patients do not exhibit elevated cerebrospinal fluid levels of norepinephrine even when blood levels may be three to five times normal.

In addition to these considerations, several other possibilities should be mentioned:

(1) Some DOPA may cross the blood-brain barrier but, in depressed patients, is not being converted to biologically active amines — i.e., dopamine and/or norepinephrine — rapidly enough or in sufficient amounts to influence CNS levels.

(2) CNS catechol amines may be increased in depressed patients following DOPA administration but may be metabolized at a rapid rate or otherwise physiologically inactivated.

(3) Brain levels of catechol amines may be elevated but exert no effects to influence the pathophysiology of the depressive state.

Despite the failure of DOPA to exert a therapeutic effect in this trial, it seems to us that more convincing evidence will be needed that DOPA administered orally does pass the blood-brain barrier before it can be concluded that the catechols — norepinephrine and dopamine — could not exert any central psychomotor effects or play any role in reversing the depressive states in man.

SUMMARY

A clinical trial of dihydroxyphenylalanine (DOPA) was undertaken as an indirect test of the catechol amine theory of depression. Previous studies have shown that DOPA is a precursor in the synthesis of catechol amines, crosses the blood-brain barrier in animals,

and reverses the behavioral and biochemical effects of reserpine. These effects are enhanced by pretreatment with a monoamine oxidase inhibitor. Assuming that the reserpinized animals represent a possible analogue of some human depressions, DOPA was administered alone and in combination with monoamine oxidase inhibitor.

The clinical trial was conducted under two conditions:

(1) Seven depressed females were treated with DOPA (600–1000 mg. daily) for up to five weeks;

(2) Five patients received a combination of phenelzine (45–60 mg. daily) and DOPA (40–800 mg. daily) for periods of one to five weeks.

There was no evidence of clinical improvement under either condition. Transient hypertensive effects were observed in the patients receiving DOPA and MAO inhibitor.

The chronic treatment with DOPA, even in large doses and when combined with MAO inhibitors, does not produce a significant change in depressed patients. This failure to achieve clinical change occurred even though biochemical analyses showed high levels of serum catechols following DOPA administration. The rise of spinal fluid catechols, however, was considerably less than that occurring in plasma, raising questions as to the passage of DOPA across the blood-brain barrier.

These findings are discussed in the light of possible differences between human and animal subjects and the discrepancies in dosages employed in this study, compared with those usually administered in animal experiments. The implications of these findings for the theory relating catechol amines to disturbed affective states are discussed.

VOL.
1
1962/

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OL.
1
62/63

VOL.
1
1962/

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BEHAVIOR OF RHESUS MONKEYS RAISED IN ISOLATION*

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OL.
1
62/63

A LARGE number of animal studies have demonstrated the important influence of experience acquired during infancy and childhood on later behavior. (For reviews see BEACH and JAYNES[1], and DENENBERG[2].) In his discussion of parameters relevant to studies concerning the effects of early experience on adult behavior patterns, KING[3] recognizes seven variables as particularly significant. Among these are included (a) the duration or quantity of the experience; (b) the type or quality of the experience, and (c) the type of performance measure obtained.

This report is primarily concerned with the effects of the second of these factors, the type or quality of the experience, on the social and manipulatory responsiveness of young rhesus monkeys. In previous studies the social behavior of adolescent monkeys raised from infancy in individual wire mesh cages was compared with the behavior of wild-born animals the same age. Laboratory-reared monkeys fought more than feral animals, groomed less and were deficient in their sexual performance[4]. In the present experiment the behavior of pubescent monkeys reared in the ordinary laboratory environment, as were the restricted subjects of the earlier experiment, is compared with the behavior of monkeys exposed from infancy to a more severe form of environmental restriction.

METHOD

Subjects

The subjects were 4 pubescent rhesus monkeys. There was one male and one female in each group. All animals were between 15 and 16 months old when the present experiment began and between 21 and 22 months old when they were permanently removed from their regular living cages for the final phase of testing. None of them had had previous exposure to any of the test situations.

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Rearing conditions

All animals were separated from their mothers at birth and housed individually in cages providing a living space 24 in. × 18 in. × 15 in. Two monkeys (restricted monkeys) were maintained in wire mesh cages in a room where they could see and hear other monkeys. They had no direct contact with other animals, however, and their contacts with human beings were limited to routine testing and caretaking activities.

The two remaining monkeys (isolates) were housed alone from birth in enclosed cages which minimized all contact with the extra-cage environment. A schematic view of an

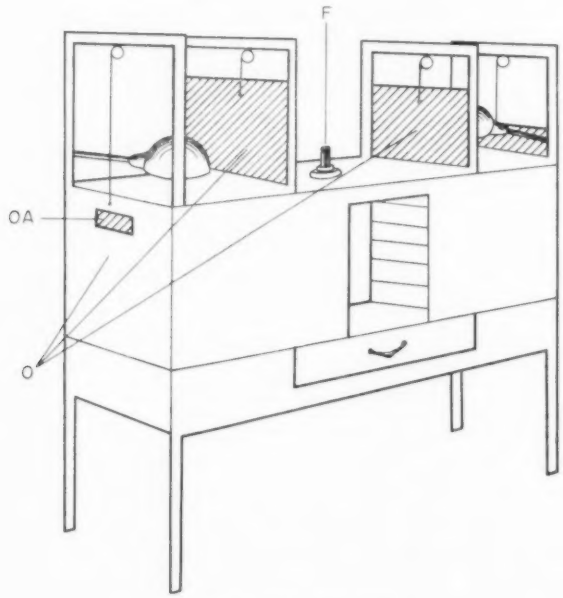

FIG. 1. Isolation cage.

OA, observation aperture; O, opaque screens; F, opening and holder for feeding tube. An opaque door covered the opening at the side of the cage.

isolation cage is shown in Fig. 1. The cage included a living space and two stimulus presentation compartments, one at each end of the living space. The ceilings of these compartments were constructed of translucent white plexiglas and illumination of the interior of the compartments and of the living space was provided by two 25-W bulbs, one placed above each compartment. Access to the stimulus presentation compartment from the living space was through horizontal bars and sliding opaque screens could be lowered between the living space and the presentation compartments, thus permitting the animals to be maintained and tested in complete social isolation[5]. Ventilation was provided by a blower which also served as a partial masking noise. The isolation cages were placed in a room which was separate from the nursery proper. The isolates were tested for manipulatory responsiveness during the first 90 days of life[5] and one of them was tested on various

VOL.
1
1962/

discrimination learning tasks starting when it was about 5 months old[6]. Performance in these situations compared favorably with data for non-isolated monkeys of similar age.

Apparatus

Until the final phase of testing the monkeys were observed in a chamber 6 ft long, 2 ft wide and 30 in. high. It was framed in angle iron and had a front of clear plastic. A sliding opaque door could be lowered to divide the cage into two sections, each 3 ft long. For competitive food-getting tests a short length of tubing with a cup formed at one end was inserted at each end of the chamber. For the last phase of testing the monkeys were placed in pairs in expanded metal cages (30 in. × 30 in. × 30 in.) within a colony room. The cages were shielded to prevent visual contact with other animals. One-way vision screens were used throughout to prevent the subjects from seeing the observer.

OL.
1
62/63

Procedure

The experiment was conducted in four phases, shown in Table 1. In Phase I (homogeneous pairs) isolates and restricted monkeys were paired only with each other. One pair

TABLE 1. EXPERIMENTAL SCHEDULE

Date	Phase	Original housing	
6/17 to 7/26	I	Homogeneous pairings	Fifteen 45-min. sessions/pr.
7/30 to 9/27	II	All pairings	Fifteen 45-min. sessions/pr.
10/2 to 11/27	III	Competitive food-getting	Five 20-trial sessions/pr.
		Caged in Pairs	
12/9 to 12/22	IV	Homogeneous pairings	Twenty 5-min. sessions/pr.
12/23 to 1/19		Mixed pairings	Twenty 5-min. sessions/pr.

was tested a day for a total of 15 sessions a pair. The animals were introduced at opposite ends of the chamber with the center door lowered. After 5 min the door was raised and the subjects were observed for 45 min. Social interactions were recorded on a continuous ink-writer according to a method described elsewhere[4]. Procedures in Phase II (all pairs) were identical to those for Phase I, except that pairings were made across as well as within the rearing condition variable. Two pairs were tested daily until each of the six possible pairs had been observed on fifteen 50-min sessions. On sessions 3 to 15 of Phase II a count was obtained of individual locomotor activity during the testing period. For this purpose the cage floor was marked off into 18 in. × 24 in. sections and a counter was advanced each time an animal entered a section up to the midline of its body. On the last five sessions all manual and oral contacts with the environment were noted. Phase III tested competitive food-getting. Each of the six pairs was tested for five sessions. A total of 20 grapes was delivered in each session, with the position of the rewarded food chute alternating by blocks of five trials.

The original housing was maintained through Phase III. The monkeys were brought to and from the observation chamber in small carrying cages, which for the isolates were completely enclosed. Upon completion of Phase III, the animals were housed in pairs in expanded metal cages. The pairs were homogeneous during the first two weeks and new pairs were formed every two weeks. Each pair was observed for a total of twenty 5-min sessions, five times in the morning, ten times in the early afternoon and five times after 9 p.m. Behavior was recorded by 15-sec intervals on a time-ruled check sheet[10]. During the first (homogeneous) pairing a 13-in. furnace chain with a ring at the end was attached to a counter bolted to the top of each cage to provide data on manipulatory activity.

RESULTS

Homogeneous pairings

The isolates appeared to be traumatized by the situation and spent the majority of the time crouching at opposite ends of the cage, clutching themselves and rocking. The female (No. 19) usually sat in the corner facing away from her partner. As she rocked she frequently struck her head against the wall with enough force to shake the cage. The male's (No. 20) behavior was similar except that he more often looked about and occasionally lipsmacked, drew back his ears and vocalized. The formal criterion of a social approach (within 6 in. of the partner) was met on only 25 occasions (five sessions). In almost every instance approach appeared to be adventitious. For example, on session 9 when the first approach was scored both animals were sitting next to the center door before the session started and fell together as it was raised. They broke apart at once. On a few other occasions approach occurred during a burst of activity in which one or both monkeys would dash frantically across the cage, sometimes colliding in passing. The cause of these episodes is unknown. They lasted only a few seconds and the animals quickly returned to their usual crouching postures. The only clear instance of a response directed specifically toward the partner occurred on session 12. Following a burst of activity both animals came to rest on the same side of the cage. During the remainder of the session the male advanced a few inches at a time toward the female until they were about a foot apart. He then leaned toward her several times and gently touched her head. She made no response to contact initially, then withdrew.

The behavior of the restricted monkeys contrasts sharply with this picture. Locomotor and manipulatory activity were high throughout. Although the restricted monkeys also displayed the syndrome of crouching, self-clasping and rocking, this comprised a much smaller portion of their total behavior than it did for the isolates. Their social behavior conformed in most respects to the general pattern described for restricted monkeys[4]. They were scored with 527 approaches and both animals exhibited play, grooming and aggression. On a few occasions the male (No. 23) attempted unsuccessfully to mount the female (No. 22), but he more often engaged in autoerotic behavior, usually by thrusting against his leg. He frequently became highly excited and danced about the cage, biting himself and pulling at his hair. These displays usually culminated in an attack on the female. At first aggression was shown by both animals, but by session 3 it was apparent that the male was dominant

VOL.
1
1962/

and thenceforth he initiated most of the approaches and all of the aggression, while the female generally withdrew from contact. Social facilitation of environmental manipulation[4] occurred on 91 occasions and was displayed by both animals. The female, however, usually waited until the male ceased to manipulate and had moved away before approaching the scene of his activity and engaging in similar behavior.

All pairings

When tested together in Phase II the restricted monkeys showed no important change from the pattern already described. The male continued to be the aggressor and made 502 approaches, compared to 33 for the female. Both animals received high scores for locomotion (No. 22 = 6910; No. 23 = 4900) and for manipulation of the environment (No. 22 = 279; No. 23 = 617). The isolates also behaved together much as they had during the previous phase. They were scored with 12 approaches (on five sessions), all apparently adventitious. As would be expected, locomotor activity was low (No. 19 = 8; No. 20 = 89), and manipulation of the environment was infrequent (No. 19 = 22; No. 20 = 14). In mixed pairings the behavior of the isolates reflected the activities of their partners. With the active and aggressive restricted male the isolates were initially passive and either submitted to rough treatment or made ineffectual attempts to push him away. They showed no counter-aggression. Within a few sessions both isolates adopted a pattern of withdrawing whenever the restricted male approached. This resulted in high activity scores and in rank-order correlations greater than 0·90 between their withdrawal responses and his approaches. Because the restricted female made few approaches, the locomotor scores of the isolates when paired with her were only slightly higher than when they were paired with each other. Table 2 presents data for locomotion and environmental manipulation for each isolate-restricted pair.

TABLE 2. TOTAL FREQUENCY OF RESPONSES FOR MIXED PAIRS. PHASE II

	Pairs							
	A		B		C		D	
	19(I)	22(R)	19(I)	23(R)	20(I)	22(R)	20(I)	23(R)
Locomotion	56	662	2453	3906	101	912	3025	3096
Manipulation	36	58	47	493	8	105	10	430

Competitive food-getting tests

Little new information was yielded by competitive testing. In mixed pairings the restricted monkeys obtained 81 per cent of the food. The male entered both sides of the cage freely with all partners and clearly dominated the situation. The restricted female was more cautious. When paired with the restricted male she took food only when he was away from the food chute and always withdrew when he approached. She took all of the food delivered to her side of the cage when she was with the isolate male and she made hesitant approaches toward his side of the cage which caused him to vocalize, deterring her from going further. She entered both sides of the cage when paired with the female isolate and received all of the

food. Both isolates tended to remain at one end of the cage unless approached by another animal and the primary difference between them was that the male took food when it was uncontested, while the female remained crouching almost continuously and took food only once.

Observations in living cages

During the entire period in which they were together the isolates generally avoided each other and were much less active than the restricted monkeys. Table 3 presents totals for

TABLE 3. TOTAL FREQUENCY OF RESPONSE FOR HOMOGENEOUS PAIRS. PHASE IV

	Isolate	Restricted
Locomotion	175	512
Crouch	344	202
Initiates Contact	4	64
Manipulates Environment	141	251
Manipulates Chain	218	5248

VOL. 1 1962/

homogeneous pairs for measures of crouching, locomotor activity, initiation of social contacts and manipulation of the environment and chain. Table 4 presents similar data on each animal for mixed pairings. Data are also included for aggression, withdrawal from

TABLE 4. TOTAL FREQUENCY OF RESPONSES FOR MIXED PAIRS. PHASE IV

	Pairs							
	A		B		C		D	
	19(I)	22(R)	19(I)	23(R)	20(I)	22(R)	20(I)	23(R)
Locomotion	77	257**	209	365**	178	275*	80	262**
Crouch	275	177**	109	50*	211	104**	304	167
Initiates Contact	1	3	0	162**	0	69**	0	111**
Aggression	0	0	0	113**	0	43**	0	69**
Passive	3	0	77	0**	24	0**	32	0
Withdrawal	37	0**	203	0**	92	6**	73	0**
Grimace	3	0	110	0**	56	0**	69	0**
Manipulation	86	94	16	172**	75	112*	20	114**

* $p<0{\cdot}05$
** $p<0{\cdot}01$

social contact, passive acceptance of social contact and grimaces (believed to indicate fear or submission[7]). To provide some indication of the consistency of differences between members of a pair, sign tests were performed comparing responses over twenty sessions. The restricted monkeys received higher scores for locomotor activity, manipulation of the environment, and all social responses except withdrawal. The isolates were consistently higher in withdrawal, passive acceptance of social contact, crouching and grimaces.

Following the final series of observations the animals were separated and housed indi-

vidually in expanded metal cages in a room with other monkeys. Non-systemic observations of the isolates made over a period of months gave no evidence of any important change in their behavior. One of us (R. R. Sponholz) had an opportunity to observe the isolates in social pairings after they had been exposed to the normal laboratory environment for about two years. Their behavior was essentially similar to the patterns already described.

DISCUSSION

While the number of animals used in this experiment is small, the results suggest that monkeys kept in isolation until early adolescence are severely and persistently handicapped in their ability to cope with other monkeys and with novel situations. The isolates' behavior can perhaps best be described as a form of traumatic withdrawal. Crouching was their characteristic posture during more than 1000 hr of exposure to the test situations. Few responses were directed toward other animals or the physical environment and the most common reactions to social contact were submission or flight.

It should be emphasized that the behavior of neither group was normal, compared to wild-born monkeys. All animals displayed the syndrome of crouching, self-clasping, thumb-sucking and stereotyped rocking which is characteristic of socially deprived monkeys and apes, particularly in stressful situations[8–11]. Thus, the important contrast between groups is not in the presence or form of these behaviors, but rather in the lack of other responses in the isolates. This is especially interesting because the isolates gave no indication of unusual behavioral constriction when they were observed and tested while living in their original isolation cages.

The persistent failure of the isolates to adapt to the extra-cage environment is probably related to two factors: One of these is the age of the animals when they were first removed from isolation (early adolescence) and the other is the contrast between the rearing environment and the test situations. While the specific test conditions used in this experiment were new to both groups, the restricted monkeys had experienced from birth a more complex and changing environment, including some exposure to situations other than the living cage, and they had had almost continuous visual contact with other monkeys. This experience was presumably a major factor facilitating their adjustment to the test situations.

SUMMARY

1. Two rhesus monkeys (isolates) were raised in enclosed isolation cages from birth until early adolescence (16 months). Two additional monkeys of the same age, raised routinely in wire mesh cages, were used as a comparison group (restricted monkeys).

2. Isolates were paired with each other and with restricted monkeys in various phases of the experiment and in all received more than 1000 hours of exposure to the test situations.

3. The isolates appeared to be traumatized by the extra-cage environment. Crouching was their characteristic posture throughout the experiment. Few responses were directed toward other animals or the physical environment and the most common reactions to social contact were submission or flight.

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VOL.
1
1962/

OL.
1
62/63